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Effect of Tetraethyl Lead on Food and Water Intake in the Rat

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CZECH, D. A., J. C. SCHMIDT AND J. M. STONE. *Effect of tetraethyl lead on food and water intake in the rat.* PHARMAC. BIOCHEM. BEHAV. 5(4) 387–389, 1976. – The effect of tetraethyl lead (TEL) on food and water intake in adult male albino rats was studied. Animals received 1, 4, 7, 10, or 13 mg/kg body weight of TEL in peanut oil, or a peanut oil placebo, via either intragastric (IG) intubation or intraperitoneal (IP) injection. For food intake, route of administration was a significant factor and, compared to baseline levels, food intake was significantly depressed at dosage levels of 7, 10, and 13 mg/kg for both IP and IG administration. Further, the time course of food intake differed significantly across route of administration. Water intake was also significantly depressed at 7, 10, and 13 mg/kg, but route of administration was not a critical factor. Results were discussed in relation to clinical and experimental data on lead intoxication, and were viewed as severely limiting the utility of employing food and/or water as motivational variables in assessment of behavioral effects linked to TEL poisoning.

Tetraethyl lead Lead poisoning Food intake Consummatory behavior Water intake

LEAD intoxication has long been recognized as a major health problem, and considerable attention has been directed toward investigating the effects of both organic [8, 13, 16] and inorganic [6, 10, 12, 14, 20, 22] lead compounds on various organ systems. In contrast, systematic investigations of effects of lead on behavior have been relatively few in number [2, 4, 5, 21].

In a recent study, Avery *et al.* [2] reported that intragastric administration of 10 mg/kg body weight of tetraethyl lead (TEL) significantly depressed bar press responding under a food reward contingency in male albino rats. These authors further stated, however, that while severe anorexia was not indicated at this dosage level, some confounding by motivational variables remained a possibility. Preliminary research from our laboratory indicated that significant decreases in both food and water intake follow intragastric administration of 10 mg/kg of TEL in both male and female albino rats. In light of these observations, it is apparent that more information on this critical question is essential. The present study was conducted to further examine the extent to which TEL affects food and water intake. A range of dosage levels and two standard routes of administration were employed.

METHOD

Animals

Ninety-six male Sprague-Dawley rats (Holtzman) ranging in age from 106–109 days and weighing from 330–382 g at the start of the experiment were used. They were housed individually in suspended wire mesh cages in a temperature controlled room maintained on a 12 hr light-dark cycle. Ground food (Purina lab chow) in nonspill cups and tap water were available ad lib throughout the experiment.

Procedure

Upon arrival at the laboratory, animals were placed in cages and allowed an acclimation period of at least three days prior to data collection. Following the acclimation period, food and water intake to the nearest 0.5 g and body weight to the nearest gram were recorded daily throughout the experimental period. The initial four days provided pre-treatment baseline data. On the fifth day, rats were assigned to one of 12 treatment groups on the basis of pre-treatment food intake, using a randomized blocking procedure.

Groups were formed according to dosage level and route of administration in the following manner. Five groups of eight rats each received an intraperitoneal (IP) injection of 1, 4, 7, 10, or 13 mg/kg body weight of TEL dissolved in peanut oil, and a sixth group received a placebo injection of peanut oil as a control. Six additional groups of 8 animals each received the same dosage levels of TEL or a placebo control via intragastric (IG) intubation. Lead concentration was 2 mg/ml of peanut oil (w/v). Placebos were equivalent in volume to loads received by animals in the 10 and 13 mg/kg TEL groups. In order to facilitate data collection with a relatively large number of subjects, animals were run in two squads, spaced approximately three weeks apart, with one-half of the animals from each group being run in each squad. Food and water intake and body weight were recorded for an additional nine days after lead treatment; however, data from the ninth day was not included in any of the analyses. The experimental period was partitioned into three blocks of four days each, designated respectively as pretreatment period (PRE), posttreatment Days 1–4 (POST-1), and posttreatment Days 5–8 (POST-2). Daily food and water intake were converted to g/100 g of body

weight, and both response measures were evaluated separately with repeated measures analyses of variance (ANOVA) and/or covariance (ANOCOV) procedures, and Duncan's multiple range tests.

RESULTS AND DISCUSSION

Mean food intake, expressed as g/100 g of body weight is presented in Fig. 1, each mean representing a block of four days. The ANOVA revealed significant changes in food intake as a function of dosage level, $F(5,72) = 20.38$, $p<0.001$, route of administration, $F(1,72) = 13.69$, $p<0.001$, blocks of days, $F(2,192) = 108.31$, $p<0.001$, and squads, $F(1,72) = 5.02$, $p<0.05$. First order interactions of dosage level × route of administration, $F(5,72) = 3.55$, $p<0.01$, dosage level × blocks of days, $F(10,192) = 11.40$, $p<0.001$, route of administration × blocks of days, $F(2,192) = 18.50$, $p<0.001$, and blocks of days × squads, $F(2,192) = 4.99$, $p<0.01$, were also significant. The two squads were distinctly different on preinjection food intake; however, this difference decreased across blocks of days. Squads was not a significant factor with the other treatment variables.

As shown in Fig. 1, mean food intake was lower following TEL administration than it was prior to treatment. Distinctly different patterns, however, can be seen with different routes of administration; at dosage levels of 4 mg/kg and higher, IG intubation resulted in a more pronounced initial depression (POST-1) of food intake than did IP injection during the POST-1 period, but was followed by some recovery as evidenced by a lesser depression for IG groups during the POST-2 period. This partial recovery was not evident in groups receiving their lead load IP, with the single exception of a minor upward shift in the 4 mg/kg IP group.

Duncan's multiple range tests were employed to make individual comparisons. Tests show that with IG intubation, food intake dropped significantly for dosage levels as low as 7 mg/kg [7, 10, and 13 mg/kg, all $p<0.001$). For the 7 mg/kg IG group, food intake returned to near the pretreatment level during POST-2, as reflected by a significant shift between POST-1 and POST-2 ($p<0.005$). The reversals between POST-1 and POST-2 for groups receiving the larger doses, namely 10 and 13 mg/kg, were not significant. For these two groups, food intake during the POST-2 period remained significantly lower than the PRE period (both $p<0.001$). In contrast, IP injection of lead resulted in a significant reduction in food intake during the POST-1 period only at a dosage level of 13 mg/kg ($p<0.05$). Even at 13 mg/kg the drop in intake associated with IP administration is less than occurred with IG intubation as low as 7 mg/kg. By the POST-2 period, however, mean intake for the 7, 10, and 13 mg/kg groups had all decreased significantly as compared to pretreatment levels ($p<0.01$, $p<0.05$, and $p<0.001$ respectively). The relatively more severe initial effects associated with IG administration are consistent across all dosage levels 4 mg/kg and higher. It is clear that this effect cannot be attributed simply to factors associated with intragastric manipulation in that control animals receiving a comparable amount of peanut oil alone (equivalent in volume to that received by animals in the 10 and 13 mg/kg groups) did not exhibit this effect. It is interesting to note that signs of gastrointestinal discomfort are sometimes associated with accidental lead intoxication [3,23].

Avery *et al.* [2] reported that unpublished findings

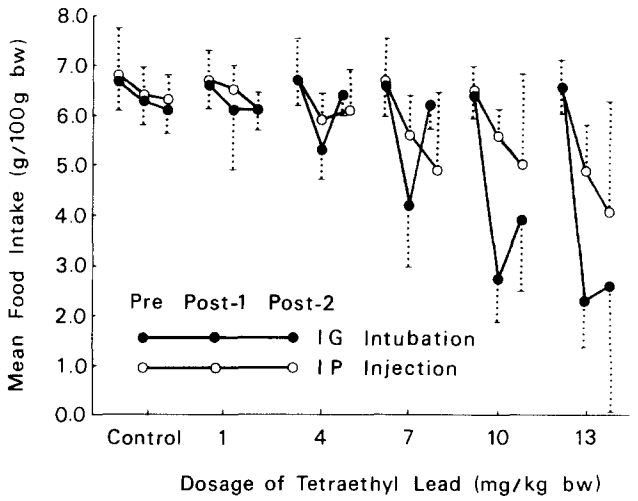

FIG. 1. Mean food intake across pre- and posttreatment periods for control and lead treated groups for both IP and IG administration. Each mean represents a block of four days. Vertical broken lines and brackets indicate one standard error.

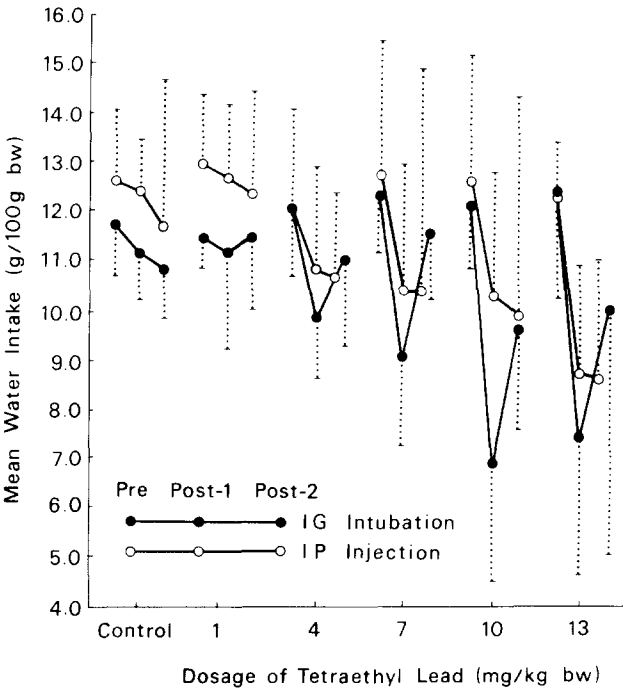

FIG. 2. Mean water intake across pre- and posttreatment periods for control and lead treated groups for both IP and IG administration. Each mean represents a block of four days. Vertical broken lines and brackets indicate one standard error.

indicate that TEL administered intragastrically has little effect on food intake for dosages up to 13 mg/kg; present results, on the other hand, clearly show that dosages as low as 7 mg/kg can result in significant depression of food intake for at least several days.

These findings are generally in accord with the clinical literature, which often reports loss of appetite as a characteristic symptom of lead poisoning in humans [1,7]. Anorexia has also been reported in cases of lead poisoning in domestic animals [9,11].

Figure 2 shows mean water intake, expressed as g/100 g

of body weight. As with food, each mean represents a block of four days. The ANOVA yielded significant effects for dosage level, $F(5,72) = 2.89$, $p<0.05$, blocks of days, $F(2,192) = 68.99$, $p<0.001$, and squads, $F(1,72) = 15.24$, $p<0.001$, while the main effect of route of administration was not significant ($p=0.059$). Highly significant first order interactions were found for blocks of days × dosage level, $F(10,192) = 6.51$, $p<0.001$, and blocks of days × route of administration, $F(2,144) = 10.31$, $p<0.001$.

Inspection of Fig. 2 shows that the pretreatment water intake means varied considerably across both dosage level and route of administration. It is clear that the assignment of animals to treatment groups by a random blocking technique based on pretreatment food intake resulted in failure to generate equivalent groups with respect to fluid intake. In order to statistically control for pretreatment variability, water intake data were subjected to an ANOCOV procedure with repeated measures on blocks of days, with the covariate factor being pretreatment fluid intake. As with the ANOVA, the ANOCOV yielded a significant effect for dosage level, $F(5,71) = 10.65$, $p<0.001$. Neither squads nor route of administration were significant. Duncan's multiple range tests pointed to significant differences between the covariate (PRE-period) and variate (postinjection period) adjusted means for water intake at the 7, 10, and 13 mg/kg dosage levels (all $p<0.001$).

It is noteworthy that at least half of the animals in the 10 and 13 mg/kg groups exhibited one or more behaviors observed with TEL intoxication in animals [8, 18, 19]. These include lethargic behavior, trembling, ataxia, fecal soiling, gnawing on cage parts, aggressiveness, sporadic violent jumping, and seizure-like convulsions. Several animals also exhibited self-mutilation of the feet and/or tail, a behavior previously reported by Schroeder *et al.* [19]. Further, fecal soiling was observed only in IP animals, while self-mutilation was observed only in animals receiving their lead load IG. Some of these behavior patterns have also been reported in cases of lead poisoning in humans [15, 17]. The full extent of these behavior patterns, however, is not known, since no attempt was made at systematizing such observations.

In general, the present study provides additional needed information about the extent to which TEL can affect aspects of consummatory behavior. Hopefully, future research will shed some light on the mechanisms involved, as well as extending investigations to other lead compounds. It is also clear that use of food or water as motivational variables is contraindicated for assessing effects of TEL on behavior at dosage levels at least as low as 4 mg/kg owing to potential confounding. Further research is needed to determine if lower dosages can be effectively employed in behavior studies.

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