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The Effects of Various Barbiturates on LiCl Induced Taste Aversion[1,2]

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JOLICOEUR, F. B., M. J. WAYNER, A. D. MERKEL, D. B. RONDEAU AND R. B. MINTZ. *The effects of various barbiturates on LiCl induced taste aversion.* PHARMAC. BIOCHEM. BEHAV. 12(4) 613–617, 1980.—The effects of various barbiturates on LiCl induced taste aversion were examined. Rats were adapted to a 23 hr and 50 min water deprivation schedule. On the Treatment Day, animals were offered a novel 0.125% saccharin solution and then administered 3.0 mEq/kg LiCl. The saccharin solution was presented again on three subsequent Test Days. Fifteen minutes prior to drinking on the first Test Day animals were injected subcutaneously with either 10, 30, and 50 mg/kg Amobarbital, 3, 9, and 15 mg/kg Pentobarbital, 40, 80 and 120 mg/kg Barbital, or 1, 3, and 9 mg/kg Hexobarbital. Results indicate that only 30 mg/kg of Amobarbital and 15 mg/kg of Pentobarbital significantly attenuated the magnitude of taste aversion.

LiCl Taste aversion Drinking Barbiturates Amobarbital Pentobarbital Barbital Hexobarbital

BARBITURATES are traditionally classified as hypnotics and sedatives. They comprise a wide variety of compounds which are all derivatives of barbituric acid. Barbiturates are usually divided on the basis of the duration of their respective hypnotic actions. For example, barbital and phenobarbital are classified as long acting; amobarbital and pentobarbital as short to intermediate acting; and hexobarbital as ultrashort acting [2].

Some barbiturates are well known dipsogenic agents. This property has been most extensively studied for phenobarbital. When injected subcutaneously in amounts below the hypnotic dose, phenobarbital increases water consumption of rats under a variety of experimental conditions [1, 12, 13, 14, 16]. Phenobarbital also enhances the consumption of mildly aversive liquids such as 3% saline solutions and 7% ethanol solutions [1,3]. Investigations of the effects of other barbiturates on water drinking reveal that both barbital and pentobarbital substantially increase drinking, while amobarbital and hexobarbital are without appreciable effects [8, 10, 12, 13]. The most effective dipsogenic doses for barbital and pentobarbital are 80 and 9 mg/kg, respectively [12].

The results of two previous studies indicate that phenobarbital can attenuate significantly taste aversion induced by either LiCl or x-radiation [4,5]. Therefore it seemed necessary to determine if this effect is specific to phenobarbital or if it can be produced by other barbiturates. The present experiment investigated the effects of barbital, pentobarbital, amobarbital and hexobarbital on LiCl induced taste aversion. Three doses of each barbiturate were studied: 40, 80, and 120 mg/kg barbital; 3, 9, and 15 mg/kg pentobarbital; 10, 30, and 50 mg/kg amobarbital; and 1, 3 and 9 mg/kg hexobarbital. As in the previous study on the taste aversion attenuating effect of phenobarbital, taste aversion was accomplished by injecting 3.0 mEq/kg LiCl following the consumption of a novel saccharin solution [4].

METHOD

Animals

One hundred and fifty-six Long-Evans female hooded rats were purchased from Blue Spruce Farms, Altamont, NY. They were placed in individual living cages in a temperature controlled room having a 12 hr light-dark cycle. At the beginning of the experiment, body weights ranged from 175–275 g. Animals were separated into 26 groups of six animals each.

Procedure

After four days of adaptation, animals were water deprived for 23 hr and 50 min and placed on a daily 10 min drinking schedule. On Day 10, the Treatment Day, animals were given a 0.125% Na saccharin solution during the 10 min drinking session. Immediately following drinking, 13 groups of animals were injected subcutaneously with 3.0 mEq/kg of

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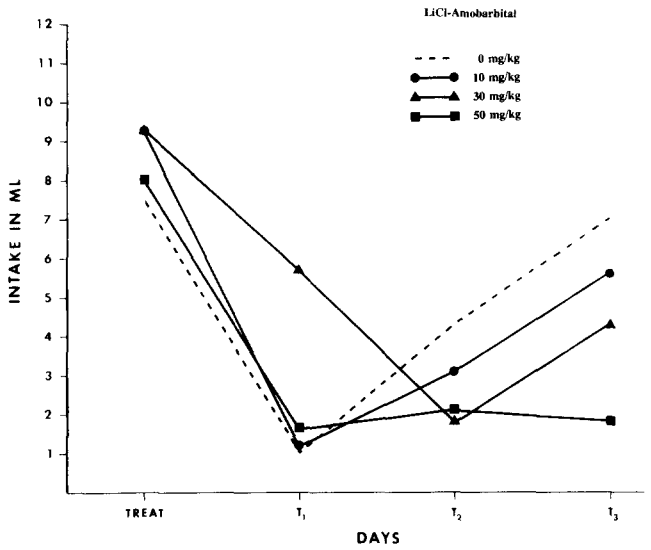

FIG. 1. Mean saccharin intakes for each group of LiCl treated animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). LiCl was administered immediately following drinking on Treatment Day. The various doses of Amobarbital were injected 15 min prior to drinking on Test Day 1.

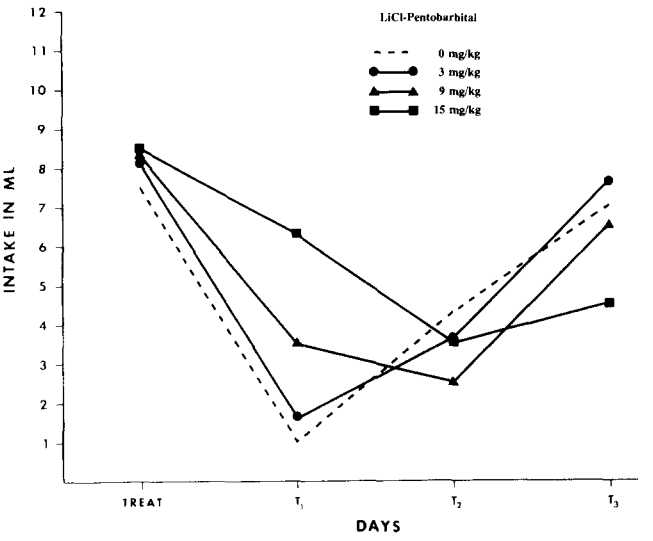

FIG. 2. Mean saccharin intakes for each group of LiCl treated animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). LiCl was administered immediately following drinking on Treatment Day. The various doses of Pentobarbital were injected 15 min prior to drinking on Test Day 1.

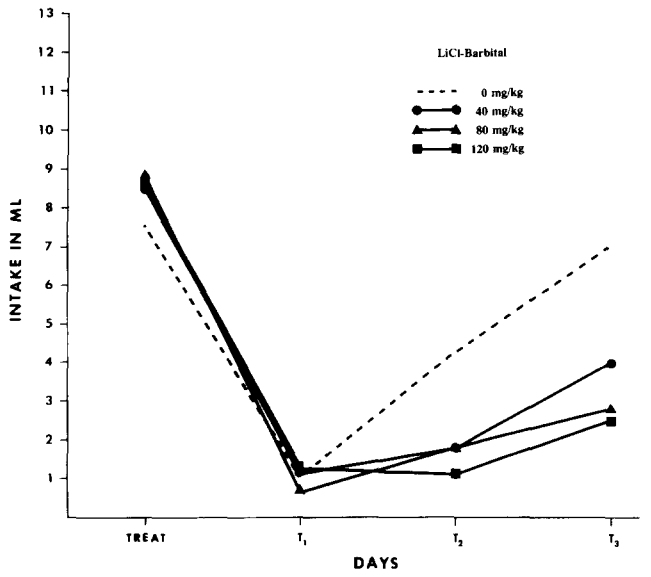

FIG. 3. Mean saccharin intakes for each group of LiCl treated animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). LiCl was administered immediately following drinking on Treatment Day. The various doses of Barbital were injected 15 min prior to drinking on Test Day 1.

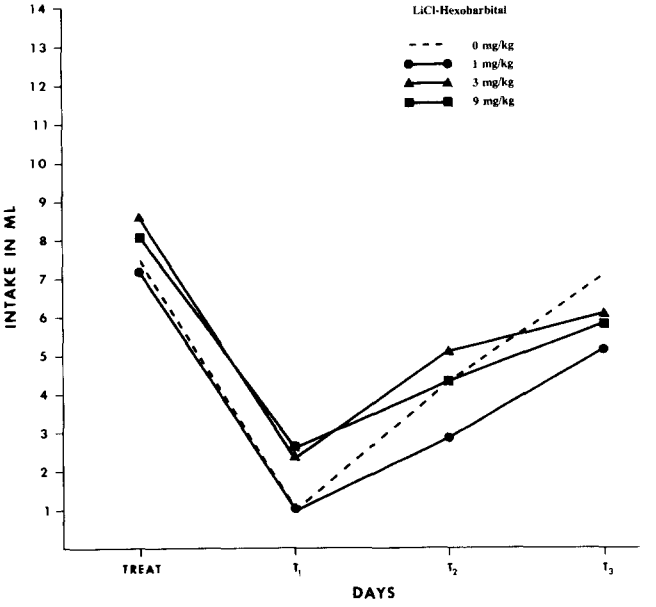

FIG. 4. Mean saccharin intakes for each group of LiCl treated animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). LiCl was administered immediately following drinking on Treatment Day. The various doses of Hexobarbital were injected 15 min prior to drinking on Test Day 1.

LiCl. The 13 other groups received 0.9% NaCl. On Days 11 and 12, water was presented during the drinking session. Then, every third day, from Day 13 to 22 animals were offered 0.125% Na saccharin during the drinking sessions. These days constituted the three post treatment Test Days. On the first Test Day, Day 13, each of the 13 LiCl treated groups received one of the following injections: 0.9% NaCl; 40, 80, or 120 mg/kg Barbital; 3, 9, or 15 mg/kg Pentobarbital; 10, 30, or 50 mg/kg Amobarbital; 1, 3, or 9 mg/kg Hexobarbital. The same injection treatments were distributed among the 13 non-treated control groups. All injections were given subcutaneously, 15 min before drinking. All drugs were dissolved in 0.9% NaCl and concentrations were adjusted so that none of the injection volumes exceeded 0.5 ml. On the remaining test days, animals were allowed to drink the saccharin solution without any other pharmacological or experimental manipulations.

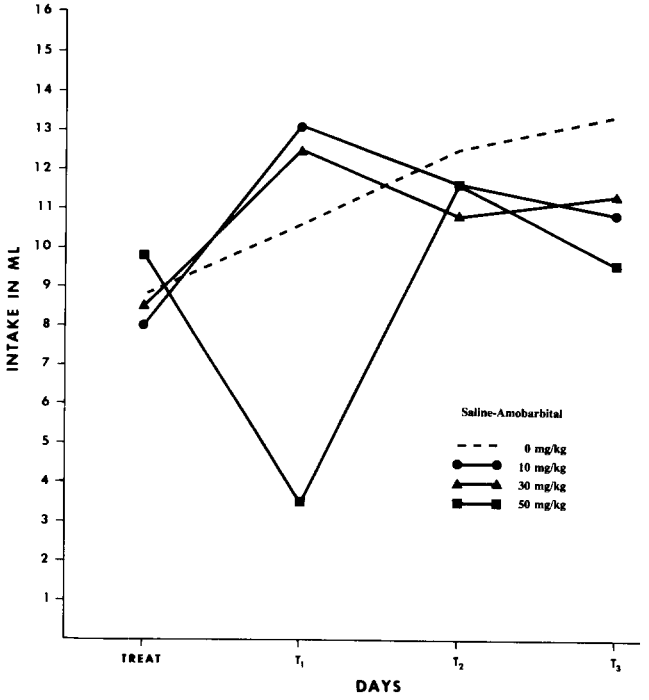

FIG. 5. Mean saccharin intakes for each group of non-treated control animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). Physiological saline was administered immediately following drinking on Treatment Day. The various dose of Amobarbital were injected 15 min prior to drinking on Test Day 1.

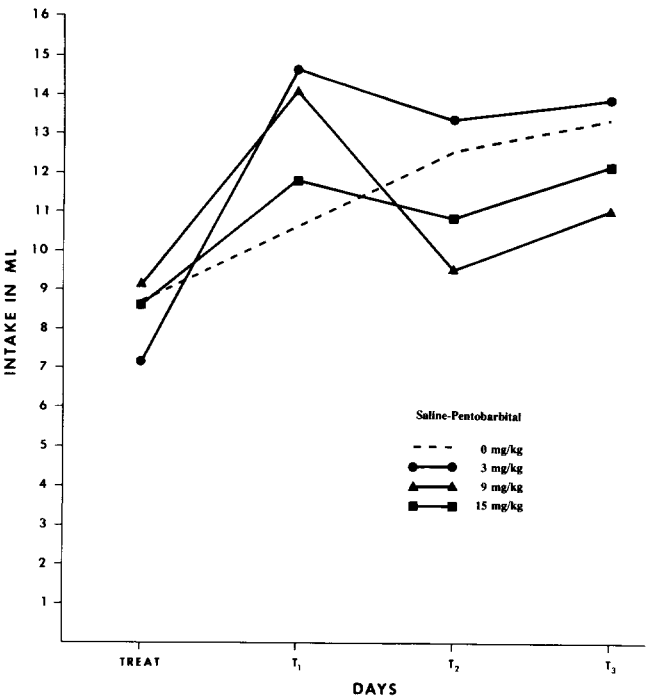

FIG. 6. Mean saccharin intakes for each group of non-treated control animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). Physiological saline was administered immediately following drinking on Treatment Day. The various doses of Pentobarbital were injected 15 min prior to drinking on Test Day 1.

All drinking fluids were presented in 100 ml graduated cylinders equipped with stainless steel ball point drinking spouts. Food, which consisted of standard Purina Rat Chow, was available throughout the experiment except for two hours following drinking on the Treatment Day.

RESULTS

Data were analyzed by means of two 13×4 ANOVA's with repeated measures on the last factor. Individual analyses were carried out for the LiCl treated groups and for the non-treated control groups. The two factors included in each analysis were Groups and Days. Each of the 13 groups receiving one particular injection on Test Day 1, contribute to one level of the Group factor. The Treatment Day and each of the three Test Days constituted the levels of the Day factor.

For the LiCl treated groups, the Day factor was significant, $F(3,36)=123.09$, $p<0.01$. The Group factor was not significant. The Group by Day interaction was significant, $F(3,195)=3.14$, $p<0.01$. This interaction was analysed by means of simple main effects analyses at each level of the Day factor. Main effect for Treatment Day was not significant. Significant main effects were found on each Test Day; Test Day 1, $F(12,180)=2.83$, $p<0.01$, Test Day 2, $F(12,180)=2.27$, $p<0.05$, and Test Day 3, $F(12,180)=2.98$, $p<0.01$. Post hoc Dunnett tests were then performed at each Test Day so that comparisons could be made between the saline injected group and the groups given a barbiturate injection on Test Day 1. These tests revealed that on Test Day 1 the 30 mg/kg dose of Amobarbital and the 15 mg/kg dose of pentobarbital significantly enhanced saccharin consumption in comparison to the saline group ($p<0.01$). No other injection had a significant effect on saccharin consumption. On Test Day 2, the saccharin intakes of the 80 and 120 mg/kg Barbital groups were significantly reduced when compared to the saline group ($p<0.01$). On Test Day 3, the saccharin consumption of the 80 and 120 mg/kg Barbital groups as well as of the 50 mg/kg Amobarbital were significantly decreased in comparison to the saline group ($p<0.01$). The results for Amobarbital, Pentobarbital, Barbital, and Hexobarbital are illustrated in Figs. 1, 2, 3 and 4, respectively, where mean saccharin intakes are presented as a function of the Treatment Day and each of the three Test Days.

The ANOVA performed on the data of the non-treated control groups revealed a significant Group effect, $F(12,65)=2.48$, $p<0.05$, and a significant Day effect, $F(3,195)=29.56$, $p<0.01$. The Group by Day interaction was also significant, $F(36,195)=4.03$, $p<0.01$. Simple main effect analyses indicated a significant main effect for Test Day 1, $F(12,180)=2.10$, $p<0.05$. No significant main effect was found on either Test Day 2 or Test Day 3. Dunnett tests performed on the data of Test Day 1 revealed that in comparison to the saline group, saccharin intakes were significantly enhanced in the 3 mg/kg Pentobarbital group and in the 40 mg/kg Barbital group ($p<0.05$). On the other hand, saccharin consumption of the 50 mg/kg Amobarbital group was significantly decreased when compared to the saline group ($p<0.05$). These results are illustrated in Figs. 5, 6, 7, and 8, where mean saccharin intakes for the Amobarbital, Pentobarbital, Barbital and Hexobarbital groups, respectively, are presented as a function of the Treatment Day and each of the three Test Days.

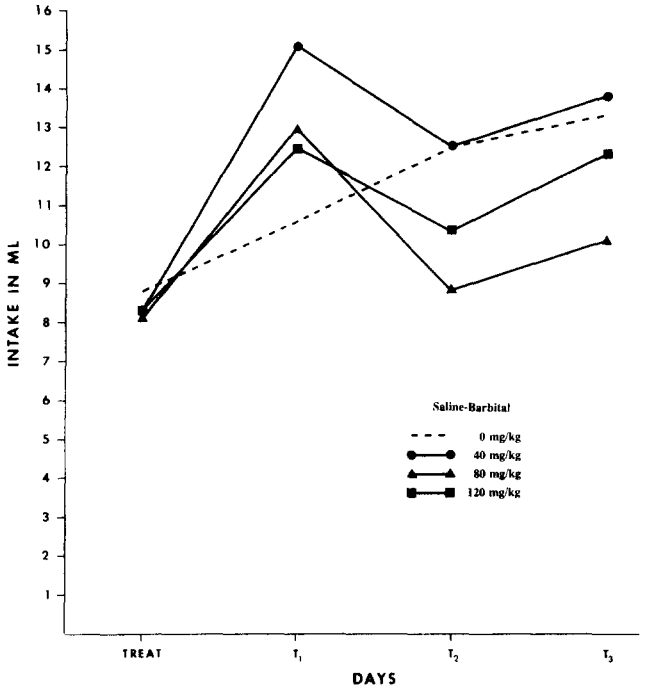

FIG. 7. Mean saccharin intakes for each group of non-treated control animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). Physiological saline was administered immediately following drinking on Treatment Day. The various doses of Barbital were injected 15 min prior to drinking on Test Day 1.

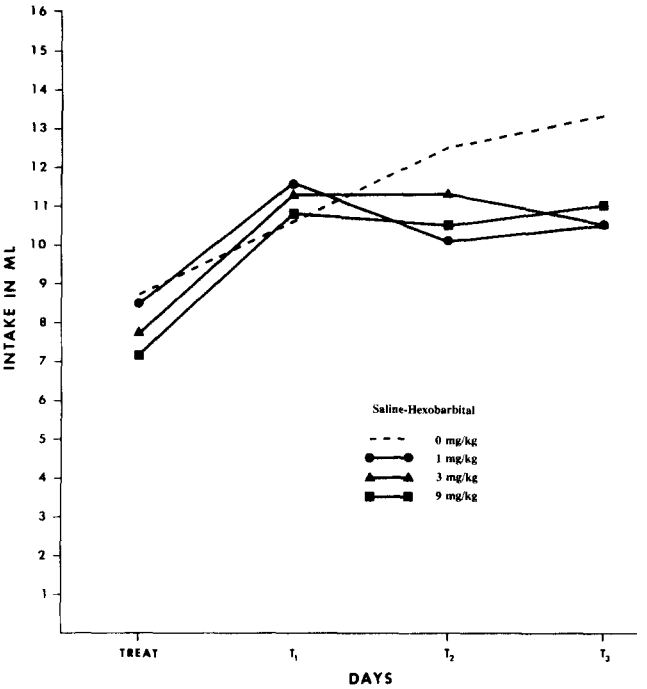

FIG. 8. Mean saccharin intakes for each group of non-treated control animals presented as a function of the Treatment Day (TREAT) and each of the three Test Days (T1–T3). Physiological saline was administered immediately following drinking on Treatment Day. The various doses of Hexobarbital were injected 15 min prior to drinking on Test Day 1.

In summary, the preceding statistical analyses indicate that in LiCl treated animals, the 30 mg/kg dose of Amobarbital and the 15 mg/kg dose of Pentobarbital significantly enhanced saccharin consumption on Test Day 1. In addition, saccharin intakes were significantly decreased on Test Days 2 and 3 in the 80 and 120 mg/kg Barbital groups and on Test Day 3 in the 50 mg/kg Amobarbital group. In the non-treated control animals, it was found that 3 mg/kg of Pentobarbital and 40 mg/kg of Barbital significantly increased, whereas, 50 mg/kg of Amobarbital significantly decreased saccharin consumption of Test Day 1.

DISCUSSION

The results of the present experiment indicate that the taste aversion attenuating effect of pentobarbital can also be produced by other, but not all barbiturates. Only 30 mg/kg of Amobarbital and 15 mg/kg of Pentobarbital significantly enhanced saccharin consumption of LiCl treated animals on Test Day 1 (Figs. 1 and 2). The other doses of these two barbiturates were without effect. Barbital and Hexobarbital in all doses tested were also ineffective in altering significantly the magnitude of LiCl induced taste aversion.

The results obtained with the non-treated control animals of this experiment indicate that saccharin intakes were significantly increased by 3 mg/kg of Pentobarbital and 40 mg/kg Barbital. No other doses of these barbiturates significantly enhanced saccharin consumption. These findings are surprising in view of the known dose effects of Pentobarbital and Barbital on water drinking in rats. The most effective doses of Pentobarbital and Barbital in increasing water consumption have been shown to be 9 mg/kg and 80 mg/kg, respectively [12]. Saccharin intakes of the non-treated control animals of this study were not affected by these doses of the barbiturates but were increased by lower doses, 3 mg/kg Pentobarbital and 40 mg/kg Barbital. These findings indicate that the dose related effects of barbiturates on drinking are dependent on the taste characteristics of the drinking fluid. Differential effects of barbiturates on water and sapid solution consumption have been reported before for Phenobarbital and Barbital [4,11]. Taste related effects have also been found for a variety of compounds, including amphetamine, atropine and methapyrilene [9], NaCl and LiCl [6,7], and chlordiazepoxide [11].

Saccharin consumption was significantly decreased by 50 mg/kg of Amobarbital. As revealed by visual observation of the animals, the depression in drinking was due to a sedative effect of this relatively high dose of the drug. Saccharin consumption was not affected by the other doses of Amobarbital nor the three doses of Hexobarbital. This was expected since these two barbiturates have been reported to have no significant effect on drinking in rats [10].

The results of this experiment demonstrate that there is no functional relation between the taste aversion attenuating effect and the dipsogenic property of a barbiturate. Amobarbital in a dose of 30 mg/kg significantly attenuated taste aversion in LiCl treated animals but did not, at any dose tested, increase saccharin intakes in the non-treated controls. None of the doses of Barbital affected taste aversion but 40 mg/kg of this barbiturate increased saccharin consumption in non-treated controls. Saccharin intakes in LiCl treated animals were increased by 3 mg/kg Pentobarbi-

tal. In non-treated animals saccharin consumption was increased by a much larger dose, 15 mg/kg. Clearly, the dipsogenic characteristic of a barbiturate is not a reliable predictor of its efficacy in attenuating taste aversion.

Finally, the administration of 80 and 120 mg/kg Barbital as well as of 50 mg/kg Amobarbital to LiCl treated animals resulted in a prolonged aversion to the saccharin solution as revealed by decreased intakes on Test Days 2 and 3. This finding is similar to that found with 40, 60 and 80 mg/kg Phenobarbital in two previously published studies [4,5]. Such an effect was not observed with Pentobarbital, suggesting that this barbiturate is less effective for inducing taste aversion. Long term aversion for saccharin was also absent in the groups injected with either 1, 3 or 9 mg/kg Hexobarbital. This is in agreement with the results of a previous study reporting no taste aversion inducing property for these doses of Hexobarbital [15].

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