SEASONAL VARIATIONS OF THE LD_{50} OF DELVINAL SODIUM FOR BOTH YOUNG AND OLD RATS * † ‡

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COPE (1) found the LD_{50} of delvinal sodium for fasted young white rats, 71 to 124 Gm. to be 170 mg. per kilogram when given by stomach tube. Molitor (2) reported the LD_{50} of this drug for fasted young rats, 120 to 180 Gm., to be 100 mg. per kilogram. Cope and Hancock (3) reported the LD_{50} of delvinal sodium for white mice to be 180 mg. per kilogram when given intraperitoneally and 190 mg. per kilogram when given by stomach tube. Hendrix (4) found the LD_{50} of delvinal sodium by stomach tube for fasted adult dogs to be only 60 mg. per kilogram.

This series of experiments was performed to determine the LD_{50} of delvinal sodium for both young and old rats by means of intraperitoneal administration of the drug. Normal and well-fed rats were used throughout the series. Animals received only one dose of the drug. The drug was dissolved in water and a fresh solution was injected intraperitoneally into more than 600 rats. The young rats ranged in age from a few weeks to about six months while the old rats were over nine months old. As soon as the animals went to sleep, they were placed in an incubator at about 85 to 90 F. to prevent chilling.

The injections were made during several different months. The first large series was begun on May 24, 1940, and continued through November 14 of the same year. It was observed that young rats died following doses of 105 to 110 mg. per kilogram of body weight during the months of June and July, and that none died after doses of less than 140 mg. per kilogram of body weight during October 1940.

The study was continued again in 1941 from March 31 to October 24, with results similar to those observed in 1940. It was difficult to explain the wide variation in the dose that would kill rats during different months of the year. Toxicity studies in this laboratory with either pentobarbital sodium or pentothal sodium had not shown such a variation (5, 6, 7).

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On continuing the study, it was noted that the following suggestion made by Shonle and associates (8) in their report in 1930 on the toxicity of barbituric acids may explain our findings: "These variations were probably due to differences in strains of rats, seasonal changes, etc."

The results of the acute toxicity experiments on young rats are given in table 1. The animals were arbitrarily divided into three weight groups. Table 1 is divided into two sections: *A*, summer months (March 30 to September 15), and *B*, winter months (September 20 to February 15). The dose of delvinal sodium was increased by increments of 5 mg. from 105 to 190 mg. per kilogram of body weight.

TABLE 1

TOXICITY OF DELVINAL SODIUM FOR YOUNG RATS *

A. SUMMER MONTHS

Weight Group	110		115		120		125		130		135		140		145	
	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D
Gm.																
25–75	7	1	8	4	8	3	12	4	12	8	13	8	5	2		
75–124	6	3	6	3	10	3	8	4	11	7	13	9	10	5	8	6
125–233	4	2	6	2	5	2	5	0	4	1	1	1				
25–233	17	6	20	9	23	8	25	8	27	16	27	18	15	7	8	6

B. WINTER MONTHS

Weight Group	135		140		145		150		155		160		165		170	
	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D
Gm.																
25–75	3	0	6	2												
75–124	2	0	10	3	8	0	3	0	4	0	7	1	11	1	13	2
125–227	4	3	10	3	13	2	20	6	12	2	8	0	2	0	1	1
25–227	9	3	26	8	21	2	23	6	16	2	15	1	13	1	14	3

I—Number of rats injected.
D—Number of rats that died following injection of delvinal sodium.
* See text for explanation of doses.

Because of space limitations, only a block of the results are presented. The LD_{50} for young rats in the first weight group seemed to be 115 to 130 mg. per kilogram in the summer while the LD_{50} for the second weight group was lower, 110 to 125 mg. per kilogram. The LD_{50} for young rats, weight 25 to 233 Gm., however, was 125 to 130 mg. for the summer months. The dose range for the winter months extended from 130 to 190 mg. per kilogram. None of the 3 animals given a dose of 130 mg. died and only 1 of 4 given a dose of 190 mg. died. The LD_{50} for young rats during the winter months seems to be above 135 mg. per kilogram and probably approaches the value of 200 mg. per kilogram.

The acute toxicity results with delvinal sodium on old rats are presented in table 2. These animals were more than nine months old. The *B* section of table 2 is a continuation of section *A*. The dose began with 70 mg. per kilogram for the summer months and with 110 mg. for the winter months. The LD_{50} for old rats seems to be about

TABLE 2

TOXICITY OF DELVINAL SODIUM FOR OLD RATS, 157 TO 530 GM.*

SECTION (A)

Season	70		75		80		85		90		95		100		105	
	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D
Summer	2	1	5	4	10	6	19	11	17	11	20	12	26	20	27	16

SECTION (B)

Season	110		115		120		125		130		135		140		145	
	I	D	I	D	I	D	I	D	I	D	I	D	I	D	I	D
Summer	29	25	27	12	10	10										
Winter	4	1	9	4	5	1	10	6	7	3	6	2	6	2	8	3

I—Number of rats injected.
D—Number of rats that died following injection of delvinal sodium.
* See text for explanation of doses.

70 to 85 mg. per kilogram for the summer months and 115 to 150 mg. per kilogram for the winter months. The results with those rats given a dose of 150 mg. are not listed in the table but 2 of 4 animals died.

DISCUSSION

Cope (1) performed his experiments on rats in Pennsylvania during the month of June 1938, and his findings correspond almost exactly with the results observed with the animals in the second weight group, table 1. Cope, however, fasted his animals and gave the delvinal sodium by stomach tube. He used 6 rats at each of the following dose levels: 120, 160 and 200 mg. per kilogram. All of his rats given 120 mg. per kilogram lived and only 2 of 6 given a dose of 160 mg. died, but the 200 mg. dose killed all of the animals. The LD_{50} was calculated by the method of Behrens as described by Burn (9).

Molitor (2), who used similar methods and technics to those of Cope (1) reported the LD_{50} to be only 100 mg. per kilogram for rats which correspond in weight to those in the third weight group in table 1. He used 5 animals at each dose level and his experiments were performed on the twentieth and twenty-fifth of January, 1938.

Hendrix (4), who did his experiments in Philadelphia during the summer of 1938, kept his adult rats for some days in an air conditioned laboratory at about 75 F. before injecting them. Six animals were used at each dose level and they were kept in their cages at the aforementioned temperature after the injections of the barbiturate. His results correspond quite closely to the results that we found in the case of the adult young rats during the cool months. The rate of absorption and the per cent of the drug absorbed, however, may have affected Hendrix' LD_{50}.

Our experiments were performed at Tuscaloosa and the animals were kept in a laboratory which became quite cold during fall and winter nights. Our findings confirm those of Shonle et al. (8), who noted variations of as much as 75 per cent in the amount of the identical lot of barbituric acid required to produce anesthesia and death when the lot was tested at varying periods throughout the year.

SUMMARY AND CONCLUSIONS

The LD_{50} of delvinal sodium has been determined for both young and old rats.

The LD_{50} was about 115 to 130 mg. per kilogram of body weight for young rats weighing 25 to 74 Gm. during the summer months. The LD_{50} for rats weighing 75 to 124 Gm. was 110 to 125 mg. per kilogram during the summer months.

The LD_{50} for young rats in the winter months seems to be above 170 mg. per kilogram.

The LD_{50} for old rats was about 70 to 85 mg. per kilogram of body weight during the summer months and above 115 to 150 mg. per kilogram during the winter months.

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