

Diet and the Duration of Thiopental Hypnosis in Rabbits.

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Malnutrition¹ and hemorrhage^{1,2} have been shown to increase the susceptibility to thiopental. Nedzel³ noted the influence of diet upon the action of phenobarbital sodium, a long acting barbiturate, and indicated that rabbits fed a mixed diet were less affected by phenobarbital than those fed oats and water. This investigation was conducted to determine whether similar dietary factors affected the shorter acting drug thiopental, which appears to be detoxified by the liver.^{4,5} The effect of nutrition upon the reactions of rabbits following a second injection of the same amount of thiopental a short time after apparent recovery from the first injection is also reported.

Materials and Methods. Thirty rabbits weighing 2.3 to 3.2 kg were given an intravenous injection of thiopental (pentothal sodium*). Each animal received 25 mg/kg of a freshly prepared 5% solution in 1 minute. Stage III anesthesia, indicated by depression of the corneal reflex, cessation of movements of the eyeball and muscular relaxation, ensued before the injection was completed. The hypnotic time was considered ended when the animal righted itself and drew its hind feet under the body into a normal sitting position. A second injection was given 1 hour after the first. A total of 76 paired injections are reported here.

Diets consisting of rabbit chow, oats and alfalfa, or oats were available with water at all times. At least 1 week elapsed after a change in diet before the hypnotic time was determined.

Results. The effect of diet upon the duration of hypnosis is indicated in Table I. All animals slept longer after the second injection than the first, indicating that some effects of the initial dose were present even after apparent recovery. Animals on diets of rabbit chow or oats and alfalfa showed an increase of 50% and 60% respectively in the duration of the second hypnotic interval. Rabbits upon a diet of oats for 1 week showed little difference in the initial sleeping time but the second hypnotic period was 90% longer than the first. The initial sleeping time increased about 65% after the animals were placed upon the oats diet for 4 weeks and the second sleeping period was more than two times that of the first. In many cases these animals were definitely depressed at the time of the second injection. Artificial respiration was often necessary immediately after the injection. In spite of this, 4 animals died. Artificial respiration was rarely necessary with animals on the other diets. Rabbits returned to a diet of chow after a 4-week interval on the oats diet showed a marked reduction in the hypnotic time within 2 weeks.

Animals on a diet of oats failed to gain weight comparable to those on the other diets, but appeared normal in other respects over a period of more than 3 months. When such animals were given chow or alfalfa, they rapidly increased in weight toward that of the control animals. The oats diet resulted in the excretion of an acid urine, pH of 6 or less as compared with pH of 9 with diet of rabbit chow and 7.5 to 8 with oats and alfalfa. When animals on oats diet were returned to a diet of chow the urine became

¹ De Boer, B., *Anesthesiology*, 1947, **8**, 375.

² Zweifach, B. W., Hershey, S. G., Rovenstine, E. A., Lee, R. E., and Chambers, R., *Surgery*, 1945, **18**, 48.

³ Nedzel, A., J., *J. Lab. and Clin. Med.*, 1937, **22**, 1130.

⁴ Shideman, F. E., Kelly, A. R., and Adams, B. J., *J. Pharm. and Exp. Therap.*, 1947, **91**, 331.

⁵ Shideman, F. E., Kelly, A. R., Lee, L. E., Lowell, V. F., and Adams, B. J., *Fed. Proc.*, 1948, **7**, 255.

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TABLE I.
Effect of Diet Upon Duration of Hypnosis Following 2 Intravenous Injections, 1 Hour Apart,
of 25 mg/kg Thiopental.

Rabbit No.	Rabbit chow		Oats and alfalfa		Oats 1 wk		Oats 1 mo.		Oats 1 mo. chow 2 wk		Oats 1 mo. with NaHCO ₃ 1 wk	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
1			15	33	26	45	42	82	22	31		
2			33	48	31	68	47	86	20	25		
3			24	34	25	62	33	72	14	25		
4			25	38	died							
5			25	38			58	135	21	35		
6			15	26			died					
7			22	34			48	246	33	47		
8			25	40			died					
9			12	29	25	48	51	98	40	59		
10			21	35	24	43	32	64				
11			20	34	25	42	died					
12			30	45	27	43	29	49	18	—		
13			30	42	26	50	51	107	16	39		
14	30*	42			26	49	43	55	19	31		
15	29	46			28	52						
16	25	39					36	101				
17	20	33					48	113				
18	24	34					32	68				
19	26	33					34	88	20	38		
20	28	41					41	—				
21	23	32					31	81	24	50		
22	27	44										
23	13	23										
24	27	45										
25	27	31										
26							48	103			39	60
27							35	64			24	35
28							43	57			19	32
29							33	101			40	59
30							32	66			26	42
Average	25	37	23	37	26	50	40	92	22	38	30	46

* Duration of sleep in minutes following intravenous injection.

alkaline within 1 week.

In a preliminary experiment to determine the relationship between acidity of urine and detoxification of thiopental 5 rabbits maintained upon a diet of oats were given sufficient NaHCO₃ orally to render the urine alkaline (pH 7.5 to 8.5). Before the addition of NaHCO₃ to their diet these animals showed an average sleeping time of 38 minutes after the first injection and 78 minutes after the second injection. One week later these animals with NaHCO₃ added to their diet showed a decrease in hypnosis to 30 minutes after the first injection and 46 after the second injection.

Discussion. That an injection of thiopental renders the animals more susceptible to subsequent injections has been reported in dogs.^{1,6} The present experiments showed that a dietary condition resulting in greater

depression after thiopental had the most pronounced effect upon a second injection. It is possible that rabbits on oats alone are in a state of malnutrition sufficient to account for their susceptibility. Preliminary work indicates that NaHCO₃ sufficient to cause the excretion of an alkaline urine in oats fed rabbits is beneficial in thiopental hypnosis.

Summary. The effect of 2 injections, 1 hour apart, of 25 mg/kg thiopental was studied in rabbits on 3 diets. Animals on a diet of oats slept much longer than those fed rabbit chow or oats and alfalfa. A diet of oats rendered the urine acid while the other diets were accompanied by excretion of an alkaline urine. NaHCO₃ fed orally to rabbits maintained on a diet of oats appeared to reduce the duration of hypnosis.

⁶ Veal, J. R., and Reynolds, C., *South. M. J.*, 1938, **31**, 649.