

EFFECTS OF ANESTHESIA ON THYROID FUNCTION OF RATS

TSUTOMU OYAMA, M.D.

RECENT investigations have called attention to a relationship between surgical trauma and altered thyroid function (1, 2, 3). Some workers have postulated that the thyroid gland is one of the important participants in the response to stress (2, 3). However, the influence of anesthesia on the activity of the thyroid gland has not been determined except for a few reports regarding the depressive effects of barbiturates (4-9).

Measuring radioactive iodine (I^{131}) uptake is one of the methods of determining thyroid function. The present study was undertaken to investigate the effect of ether and cyclopropane on the uptake of radioactive iodine in the thyroid glands of white rats, and to compare their effect with that of a known thyroid depressant thiopental sodium.

MATERIAL AND METHODS

One hundred and eight male albino rats of the Sprague Dawley strain were used in these studies. Their ration consisted of Purina Laboratory Chow and water as desired, and they were housed in a room temperature of 37 C. The rats were divided into four groups of 27 each with uniform body weight (113-146 Gm.) as shown in table 1. They were designated as control, cyclopropane, ether, and thiopental groups. The determination of thyroid uptake of I^{131} was made at 2, 4, and 24 hours after administration of radioiodine. Not less than 4 or more than 8 animals were used in each phase of the experiment.

Ethyl ether was administered for two hours to rats in a jar of 2,000 ml. capacity from a tube connected to a gas machine which passed through a rubber stopper into the top of jar. The ether was injected through a needle point into a gauze covered wire tray suspended below the rubber stopper. Depth of ether anesthesia was adjusted by diluting the ether vapor with oxygen from the gas machine or by removing the rats occasionally from the jar and allowing them to breathe room air during the experiment.

Cyclopropane was given to the rats for two hours through a tube from a gas machine in a similar manner. The level of anesthesia was maintained by the conventional method of alternating the flow of cyclopropane and oxygen intermittently. The rats were kept in a closed system in the jar throughout the administration of anesthesia.

Accepted for publication May 14, 1957. Dr. Oyama is in the Department of Anesthesiology, University of Oregon Medical School, Portland, Oregon.

The level of anesthesia for ether and cyclopropane was maintained at plane 1 or 2 of stage III. If the rats were twitching or had irregular respiration they were considered to be in stage II. If they showed little or no movement and had regular respiration they were taken to be in stage III, plane 1 or 2. If they had slow, gasping, diaphragmatic or paradoxical respiration, they were classified as in stage III, plane 3 or 4, and in stage IV if respiratory arrest occurred (10). The rats slept from 10 to 15 minutes after ether and cyclopropane anesthesia was discontinued. It took an additional 20 to 30 minutes to regain full preanesthetic activity.

TABLE 1
EFFECT OF ANESTHESIA ON THE I^{131} UPTAKE BY THE THYROIDS OF RATS

Anesthesia	Number of Rats	Hours from I^{131} Administration	Body Weight (Gm.) and Standard Error of the Mean	Thyroid Weight (Mg.)	Administered I^{131} in Thyroid		p	Significant Compared with Control
					Per Cent	Per Cent of Control		
Control	10	2	113 ± 6.3	11.5 ± 0.9	8.9 ± 1.0	(100)	—	
Cyclopropane	10	2	115 ± 12.6	10.8 ± 1.0	4.9 ± 0.9	(55)	<0.02	+
Ethyl ether	10	2	125 ± 8.8	11.8 ± 0.6	5.2 ± 0.6	(58)	<0.02	+
Thiopental	10	2	137 ± 6.3	10.6 ± 0.0	1.8 ± 0.2	(20)	<0.01	+
Control	7	4	137 ± 4.9	13.5 ± 1.4	9.4 ± 1.8	(100)	—	
Cyclopropane	7	4	139 ± 11.5	12.8 ± 0.8	8.1 ± 0.7	(86)	>0.50	—
Ethyl ether	7	4	146 ± 10.3	12.9 ± 1.2	7.2 ± 0.7	(76)	>0.50	—
Thiopental	7	4	124 ± 5.0	11.8 ± 1.0	1.4 ± 0.3	(14)	<0.01	+
Control	10	24	131 ± 9.6	9.8 ± 0.4	33.8 ± 6.3	(100)	—	
Cyclopropane	10	24	139 ± 9.6	9.6 ± 0.7	37.0 ± 3.8	(109)	>0.50	—
Ethyl ether	10	24	142 ± 9.6	10.0 ± 0.5	30.2 ± 3.0	(89)	>0.50	—
Thiopental	10	24	127 ± 6.3	9.6 ± 0.4	16.7 ± 1.6	(49)	<0.05	+

The inhibition of cyclopropane and ether on thyroid uptake of I^{131} shown in the 2-hour test became insignificant in the 4-hour and 24-hour tests. Thiopental significantly depressed thyroid uptake of I^{131} in the 2-hour, 4-hour and 24-hour tests.

Thiopental (Pentothal) was given to the fourth group by single intraperitoneal injection of 40 mg. per kg. of body weight. The rats slept from one and one half to two hours, and required from three to three and one half hours to resume preanesthetic activity. They were less active than either the ether or cyclopropane groups in the immediate postanesthetic stage.

Five minutes after beginning administration of anesthesia, 10 μ c. of I^{131} * diluted in normal saline was injected intraperitoneally. Immediately after the animals were killed with chloroform, the thyroid glands were removed, stripped of adherent tissues, and weighed with a Gram-Atic balance. No food but water as desired was given after the experiments started.

* I^{131} was prepared by Abbott Laboratories, Oak Ridge, Tenn.

The well type of scintillation counter (Reed Curtis Model LAX 16p with Reed Curtis Scintiscaller Model CX 14s) was employed for the determination of I^{131} uptake. A minimum of 6,400 counts were recorded on all samples. Correction for decay of radioactivity was applied by the conventional method. Results were expressed as percentage of the amount of injected radioiodine. The "t-test" for the significance of the difference between the means was used in the statistical analysis.

RESULTS

Cyclopropane.—Administration of cyclopropane for two hours significantly inhibited the 2-hour thyroidal uptake of I^{131} of albino rats (55 per cent of the uptake in control groups). A slight difference was demonstrated between the cyclopropane and control groups at the end of 4 hours (table 1). This difference was not considered significant. No appreciable residual effect was noted at the end of 24 hours (table 1).

Ether.—In the group having a 2-hour ether anesthesia, uptake of I^{131} was significantly inhibited (58 per cent of the uptake in control group). No salient difference was revealed between the ether and control groups on the 4-hour and 24-hour accumulation of radioiodine (table 1).

Thiopental.—The most profound depressive effect on thyroid activity was noted with thiopental anesthesia. Even the 24-hour test showed 49 per cent accumulation in comparison with the control group. At the end of the 2-hour anesthesia, I^{131} uptake of the thiopental group was only 20 per cent of the control group. These data coincide with previous reports relating to barbiturates (7-9).

DISCUSSION

Factors related to anesthesia which might influence thyroid function appear to be many. These include effects on the kidney function, blood circulation, central nervous system, hypothalamus, and other hormonal organs such as the pituitary and adrenal glands. However, consideration of these factors is beyond the scope of the present investigation.

The results of the 2-hour test, as shown in table 1, revealed the deepest inhibition of thyroid uptake of I^{131} to be in thiopental group. As was pointed out in "Material and Methods," the period of anesthesia was almost the same for all groups. Therefore, the marked depression of thyroid activity in the thiopental group cannot be attributed to any difference in the length of anesthesia.

In the 2-hour test the observed differences in uptake of I^{131} between the cyclopropane and ether groups versus the thiopental group were of statistical significance ($p < 0.01$). In the 4-hour and 24-hour tests the observed depressed uptake of the thiopental group might have

been due to the prolonged postanesthetic inactivity. However, it would appear that this depression was most likely due to the antithyroid effect of the drug.

Many investigators agree that barbituric acid directly suppresses the activity of the thyroid gland because of its chemical structure, $N-C=S$, which has antithyroid action (4-9). This prolonged effect of thiopental on the thyroid gland is of interest.

Previous observations of the effect of surgery on thyroid activity (1-3) may be due in part to anesthesia as well as surgical trauma. This investigation indicates that thiopental may be the most effective depressant anesthetic agent of thyroid activity.

SUMMARY

The present experiment was undertaken to investigate the effects of anesthesia on the thyroid gland by employing tracer doses of radioactive iodine (I^{131}) in 108 male albino rats. Results analyzing the 2-hour, 4-hour and 24-hour thyroid uptake of I^{131} revealed the following.

Cyclopropane and ether anesthesia definitely inhibited the 2-hour thyroid uptake of I^{131} . This profound influence on the thyroid became insignificant in 4-hour test. The 24-hour test indicated that there was no appreciable influence of cyclopropane or ether on the thyroid uptake of I^{131} . Thiopental administered intraperitoneally significantly depressed the thyroid uptake of I^{131} in 2-hour, 4-hour and 24-hour tests.

This investigation was supported in part by a grant from the Oregon Heart Association. The author wishes to express his appreciation to Drs. Frederick P. Haugen, Tyra T. Hutehens, and Leonard Christensen for their encouragement, helpful suggestions, and advice in the preparation of the manuscript.

REFERENCES

1. Perry, W. F., and Gemmell, J. P.: Effect of Surgical Operations on Excretion of Iodine, Corticosteroids, and Uric Acid, *Canad. J. Res. Sec. E* **27**: 320 (Dec.) 1949.
2. Goldenberg, I. S., Lutwak, L., Rosenbaum, P. L., and Hayes, M. A.: Thyroid-adrenocortical Interrelations Following Operation, *Surg. Gyn. & Obst.* **98**: 513 (May) 1954.
3. Goldenberg, I. S., Lutwak, L., Rosenbaum, P. L., and Hayes, M. A.: Thyroid Activity During Operation, *Surg. Gyn. & Obst.* **102**: 129 (Feb.) 1956.
4. Astwood, E. B., Bessell, A., and Hughes, A. M.: Antithyroid Activity of Thiobarbital, *Endocrinology* **36**: 72 (Jan.) 1945.
5. Astwood, E. B.: Some Observations on Use of Thiobarbital as Antithyroid Agent in Treatment of Graves' Disease, *J. Clin. Endocrinol.* **5**: 345 (Oct.) 1945.
6. Bartels, E. C.: Use of Thiobarbital in Treatment of Hyperthyroidism, *J. A. M. A.* **129**: 932 (Dec.) 1945.
7. Wase, A. W., and Greenspan, J.: Effect of Sodium 5-Allyl-5-(1 Methylbutyl) 2-Thio-barbiturate on Uptake of I^{131} by Rat Thyroid, *Proc. Soc. Exper. Biol. & Med.* **84**: 154 (Oct.) 1953.
8. Wase, A. W., Replinger, E., and Foster, W. C.: Effect of Anesthetic Agents on Thyroid Activity of Rat, *Endocrinology* **53**: 630 (Dec.) 1953.
9. Wase, A. W., and Foster, W. C.: Thiopental and Thyroid Metabolism, *Proc. Soc. Exper. Biol. & Med.* **91**: 89 (Jan.) 1956.
10. Mörch, E. T., Ayerigg, J. B., and Berger, M. S.: Anesthetic Effects of Ethyl Vinyl Ether, Divinyl Ether, and Diethyl Ether on Mice, *J. Pharmacol. & Exper. Therap.* **117**: 184 (June) 1956.