THE EFFECT OF EPINEPHRINE ON ANAESTHETIZED HYPERTHYROID DOGS PRETREATED WITH RESERPINE AND/OR GUANETHIDINE*

PETER KWANG-YI LEE, M D ,† JACOB S ISRAEL, M D , AND ALLEN B DOBKIN, M D

THERE IS a continuing search to find new and safer drugs to restore normal metabolism to the hyperthyroid patient and to protect the euthyroid patient from the stress of noxious stimuli to the cardiovascular system. Spontaneous cardiac arrhythmias are sometimes observed during anaesthesia in euthyroid patients, but they can occur far more frequently either in the undiagnosed or in the frankly hyperthyroid individual.^{1 2 3} Studies in hyperthyroid dogs have substantiated these clinical impressions.⁴

Reserpine and guanethidine have been used in the treatment of hyperthyroid patients to relieve some of their distressing symptoms.^{5,6} The beneficial action of both of these drugs in hyperthyroid individuals probably results from depletion of body epinephrine stores.^{7 8}

Even though reserpine and guanethidine are valuable in the treatment of patients with various diseases,^{5 6 9 10} they have been implicated as a direct cause of morbidity during anaesthesia and surgery. Terminating their use a few days before administration of anaesthesia has therefore been suggested.^{11 12}

This study was undertaken to determine whether or not the response of anaesthetized hyperthyroid dogs to a standard epinephrine challenge was altered by pretreatment with reserpine, guanethidine, or a combination of both drugs.

METHOD

Three groups of experiments were planned on each of 10 medium-sized (15–20 kg) mongrel dogs. The dogs were weighed and blood for thyroxine-iodine (T_4) by column determinations was drawn from the 10 dogs in the fasting state.¹³ Once daily, they were hand-fed Protamone® (iodinated casein with 1 per cent free iodine and 7 per cent protein-bound iodine) in gelatin capsules wrapped in meat. The dose of Protamone given was 0.3 gm/day for 6 days, 0.9 gm/day for 5 days, and 1.8 gm/day for a period of 10 days. After 21 days of therapy, blood for T_4 by column tests was drawn from these dogs.

Group I

Five of the 10 dogs were then given 7.5 mg/kg of guanethidine intravenously twice, three hours apart. On the following day, the dogs were weighed in the fasting state (mean 17.8 kg) and then anaesthetized with a sleep dose of thio-

*From the Department of Anesthesiology, State University of New York, Upstate Medical Center, Syracuse, New York

†Postdoctoral Research Fellow

pental and 20 mg of succinylcholine chloride was used to facilitate intubation. An infusion of isotonic saline was started at this time to maintain hydration and provide a route for the injection of the epinephrine challenge. Breathing was augmented with a Takaoka respirator for the maintenance of adequate pulmonary ventilation.¹⁴ The volume of ventilation was set so that the animal would receive a minute volume of 400 ml/kg body weight. Immediately following endotracheal intubation, an electrocardiogram (lead 2) was recorded on each dog while the animal was being ventilated with 100 per cent oxygen. Following the control tracing, 10 to 15 per cent methoxyflurane was volatilized with oxygen and administered to the dog from a calibrated temperature-compensated vaporizer (Pentec®). At 5-minute intervals, an electrocardiogram tracing was taken until 25 minutes of methoxyflurane anaesthesia had elapsed. Then, an intravenous challenge with 0.02 mg of epinephrine/kg body weight was administered in a solution containing 0.02 mg/ml, injected at the rate of 1 ml/sec. The electrocardiogram tracing was recorded continuously until it returned to the pre-injection configuration or the dog died of ventricular fibrillation. Because four of the five dogs in Group I died, no further animals were studied in that group.

Group II

Four of the initial 10 dogs were continued on Protamone 1.80 gm/day and, in addition, were hand-fed reserpine 35 gamma/kg/day for a subsequent period of 14 days. These dogs were then weighed (mean 17.75 kg), anaesthetized, and challenged with epinephrine as described above. Because all four of the animals studied in this group died, no further animals were studied.

Group III

One survivor of Group I, and nine fresh dogs pretreated with Protamone for 21 days, were continued on Protamone and reserpine as described for Group II. On the day before the experiment, they were also given guanethidine 15 mg/kg in divided doses as described for Group I. The next day, they were weighed (mean 16.6 kg), anaesthetized, and challenged with epinephrine as described above.

RESULTS

The type, incidence, and duration of cardiac arrhythmias that occurred after epinephrine challenge are summarized in Tables I and II.

The level of thyroxine iodine for the euthyroid dogs ranged from 0.9 to 3.0 μ g per cent with a mean of 1.7 μ g per cent. After 21 days of Protamone therapy, the thyroxine iodine determinations ranged from 4.2 to 8.7 μ g per cent with a mean of 6.4 μ g per cent.

On the day the experiments were performed, there was a 5 per cent, 12 per cent, and 5 per cent reduction in body weight of the hyperthyroid dogs in Group I, II, and III, respectively, from their control values.

TABLE I

Drugs group	Group no	No of dogs	No of anaesthetized*	Ventricular fibrillation	Ventricular premature contractions	Ventricular tachycardia	Bigeminy	Ventricular rhythm	Multifocal ventricular extrasystoles
Hyperthyroid + guanethidine	I	5†	4	3	1	1	1	1	1
Hyperthyroid + reserpine	II	4	4	4	0	0	0	0	0
Hyperthyroid + guanethidine + reserpine	III	10†	9	6	3	3	0	3	3

*Only dogs that did not sustain ventricular fibrillation are included in the calculation of type of other arrhythmias

†One dog each of Groups I and III died 1 hour after receiving 15 mg/kg of guanethidine

TABLE II

Drugs group	Group no	No of dogs anaesthetized	Ventricular fibrillation	Onset of arrhythmias (seconds after epinephrine)	Duration of ventricular tachycardia* (seconds)	Total duration of arrhythmias* (seconds)	Comment
Hyperthyroid + guanethidine	I	4†	3	12.8	See comment	0	1 dog, prolonged ventricular tachycardia—moved, unable to ascertain end points
Hyperthyroid + reserpine	II	4	4	14.8	0	0	
Hyperthyroid + guanethidine + reserpine	III	9†	6	13.8	151.3	193.3	

*Only dogs that did not sustain ventricular fibrillation are included in the calculation of duration of arrhythmias

†One dog each of Groups I and III died 1 hour after receiving 15 mg/kg of guanethidine

The mean heart rate after endotracheal intubation for Group I dogs was 105 beats/minute, for Group II, 133 beats/minute, and for Group III, 107 beats/minute. After 25 minutes of anaesthesia with methoxyflurane, the heart rate decreased at least 25 per cent in all groups. For Group I, the mean heart rate was then 65 beats/minute, Group II, 59 beats/minute, and Group III, 80 beats/minute. One dog in Group I and one dog in Group III died shortly after receiving a total of 15 mg guanethidine.

After the epinephrine challenge, the following electrocardiographic changes were seen. All of the hyperthyroid dogs developed either ventricular tachycardia or ventricular fibrillation. Three of four dogs (Group I) pretreated with guanethidine, four of four dogs (Group II) pretreated with reserpine, and six of nine dogs (Group III) pretreated with reserpine and guanethidine developed ventricular fibrillation.

The one surviving dog of Group I (hyperthyroid, guanethidine pretreatment) had a long period of ventricular tachycardia. The three surviving dogs of Group III (reserpine and guanethidine pretreatment, hyperthyroid dogs) sustained severe and prolonged ventricular tachycardias lasting an average of 151.3 seconds. In Group III, the mean duration of arrhythmias in the surviving dogs, after the epinephrine challenge, was 193.3 seconds.

DISCUSSION

The normal range for thyroxine (T_4) by column method, utilizing the anion-exchange resin Dowex-1, is 3.2 to 6.4 μg per cent in human controls, i.e., the same as for the butanol-extractable iodine method.¹³ In this study, the control value for 10 dogs was 1.7 μg per cent, with a range of 0.9 to 3.0 μg per cent. From a previous study,⁴ we observe that the PBI determinations in the control dogs were lower than normal human controls. The T_4 by column controls indicated a similar relationship between the human and dog values. In the hyperthyroid state, all of the determinations were higher than the corresponding control with the T_4 by column, averaging 6.4 μg per cent. Further, T_4 by column determinations were discontinued because the results of the tests gave an inadequate estimation owing to incomplete separation of some of the organic constituents.¹⁵

In the original plan of this study, Groups I, II, and III were to have contained 10 dogs each. When the high mortality was seen—four deaths out of the five dogs in Group I and four deaths of the four dogs in Group II—the effect was clear, so it was decided not to sacrifice the animals unnecessarily. It was obvious that carrying out the planned number of experiments would contribute little to the observation that guanethidine or reserpine in hyperthyroid dogs does not protect against epinephrine-induced arrhythmias.

In a previous study,⁴ it was seen that there is an increased incidence and severity of induced arrhythmias in anaesthetized hyperthyroid dogs. It appears that in the hyperthyroid state there is no demonstrable increase in epinephrine entering the bloodstream from the adrenal glands.¹⁶ Instead, there appears to be an increase in sensitivity to it¹⁷ and a prolongation of epinephrine action, possibly

on the basis of decreased oxidation related to a decrease in circulating amine oxidase^{18,19}

The base-line heart rate of dogs in Groups I, II, and III was slower than that of comparable dogs not pretreated with guanethidine and/or reserpine.⁴ After 25 minutes of methoxyflurane anaesthesia, the heart rate of all of these dogs decreased even further. This was evidently due to the negative chronotropic effect of guanethidine and reserpine,^{7,8} augmenting a similar effect of methoxyflurane on hyperthyroid dogs.⁴

Reserpine pretreatment causes catecholamine depletion and the resulting sympathetic depression is undoubtedly only one of the many variables which may affect the circulatory status of a patient who is to undergo anaesthesia. It seems, therefore, that it would be more useful to evaluate the situation as a whole, rather than to focus attention on reserpine medication alone.⁸ Recently, Alper and associates stated further that lowering the blood pressure with reserpine might *decrease* the anaesthetic risk in some patients.⁸

When dogs are pretreated with guanethidine and/or reserpine, they appear to have an *increased* sensitivity of the heart and blood vessels to catecholamines²⁰⁻²⁴. The reason for this supersensitivity is not completely understood.²³ Fleming and Trendelenburg have shown that supersensitivity becomes progressively greater with increasing length of reserpine therapy.²¹ They also demonstrated that development of supersensitivity requires time following depletion and that it results from inactivity of the effector organ²³ irrespective of whether such inactivity is the consequence of denervation, of loss of transmitter caused by reserpine, or of the administration of cocaine.⁸ The mechanisms for guanethidine supersensitivity may very well be the same, although recent views of Brodie suggest that these two drugs have different modes of action.²⁵ Thus, it would appear to be extremely dangerous to administer epinephrine to hyperthyroid patients, especially if they are receiving guanethidine and/or reserpine concurrently.

SUMMARY AND CONCLUSIONS

Dogs made hyperthyroid with Protamone were anaesthetized with thiopentone and methoxyflurane after pretreatment with either guanethidine and/or reserpine. They were then given a standard epinephrine challenge. Ventricular fibrillation and other severe ventricular arrhythmias were seen more frequently in all of these animals than was observed in previous studies of hyperthyroid dogs anaesthetized with methoxyflurane, but not pretreated with reserpine and/or guanethidine.

Thus, by inference from the literature reviewed and the experimental work of this paper, it would appear to be extremely dangerous to administer epinephrine to hyperthyroid patients while they are receiving guanethidine and/or reserpine therapy.

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RÉSUMÉ

Après avoir traité à la guanéthidine et/ou à la réserpine des chiens rendus hyperthyroïdiens par la Protamone, nous les avons anesthésiés au thiopentone et au méthoxyfluorane. Nous avons fait alors sur ces chiens une épreuve standard à l'épinéphrine. Chez tous ces animaux, nous avons observé des fibrillations ventriculaires et d'autres arythmies graves plus fréquemment que nous ne l'avions fait, au cours d'études antérieures, chez des chiens hyperthyroïdiens anesthésiés au méthoxyfluorane, mais non traités au préalable à la réserpine et/ou à la guanéthidine.

En conséquence, d'après les publications antérieures et le travail expérimental rapporté dans cet article, il semble très dangereux de donner de l'épinéphrine à des hyperthyroïdiens qui reçoivent de la guanéthidine et/ou de la réserpine.

REFERENCES

- 1 DELIT, C., SILVER, S., YOHANEM, S. B., & SEGAL, R. L. Thyrocardiac Disease and Its Management With Radioactive Iodine (I^{131}) *JAMA* 176 262 (1961)
- 2 HOFFMAN, I., & LOWERY, R. D. The Electrocardiogram in Thyrotoxicosis *Am J Cardiol* 6 893 (1960)
- 3 HUDSON, R. H. Toxic Goitre and Abnormal Cardiac Rhythm. *Proc Roy Soc Med* 52 810 (1959)
- 4 ISRAEL, J. S., BYLES, P. H., & DOBKIN, A. B. The Cardiac Effect of Epinephrine during Anaesthesia in Hyperthyroid Dogs *Canad Anaesth Soc J* 9 437 (1962)
- 5 CANARY, J. J., SCHAAF, M., DUFFY, B. J., JR., & KYLE, L. H. Effects of Oral and Intramuscular Administration of Reserpine in Thyrotoxicosis *New Engl J Med* 257 435 (1957)
- 6 GAFFNEY, T. E., BRAUNWALD, E., & KAHLER, R. L. Effects of Guanethidine on Triiodothyronine-Induced Hyperthyroidism in Man *New Engl J Med* 265 16 (1961)
- 7 GAFFNEY, T. E., BRAUNWALD, E., & COOPER, T. Analysis of the Acute Circulatory Effects of Guanethidine and Bretylium *Circ Res* 10 83 (1962)
- 8 ALPER, M. H., FLACKE, W., & KRAYER, O. Pharmacology of Reserpine and Its Implications for Anesthesia *Anesthesiology* 24 524 (1963)
- 9 MERRILL, J. P. Diagnosis and Treatment of Renal Hypertension of Humoral Origin *Anesthesiology* 24 479 (1963)
- 10 LEWIS, J. A., & KAVELMAN, D. A. Long-term Follow-up of Patients with Hypertensive Disease Treated with Guanethidine *Canad Med Assoc J* 88 1010 (1963)
- 11 ZIEGLER, C. H., & LOVETTE, J. B. Operative Complications after Therapy with Reserpine and Reserpine Compounds *JAMA* 176 916 (1961)
- 12 CRANDALL, D. L. The Anesthetic Hazards in Patients on Anti-hypertensive Therapy *JAMA* 179 495 (1962)
- 13 PILEGGI, V. J., LEE, N. D., GOLUB, O. J., & HENRY, R. J. Determination of Iodine Compounds in Serum I. Serum Thyroxine in the Presence of Some Iodine Contaminants *J Clin Endocrinol & Metab* 21 1272 (1961)
- 14 DOBKIN, A. B. The Takaoka Respirator for Automatic Ventilation of the Lungs *Canad Anaesth Soc J* 8 556 (1961)
- 15 Personal Communication from Dr. V. J. Pileggi (May 14, 1963)
- 16 ROGOFF, J. M., & CORTELL, R. Epinephrine Output from the Adrenal Glands in Experimental Hyperthyroidism *J Lab & Clin Med* 26 981 (1941)
- 17 MURRAY, J. F., & KELLY, J. J., JR. The Relation of Thyroidal Hormone Level to Epinephrine Response. A Diagnostic Test for Hyperthyroidism *Ann Int Med* 51 309 (1959)
- 18 SWANSON, H. E. Interrelations between Thyroxine and Adrenaline in the Regulation of Oxygen Consumption in the Albino Rat *Endocrinology* 59 216 (1956)
- 19 SPINKS, A., & BURN, J. H. Thyroid Activity and Amine Oxidase in the Liver *Brit J Pharmacol* 7 93 (1952)

20. FLEMING, W. W. Supersensitivity of the Cat Heart to Catecholamine-Induced Arrhythmias Following Reserpine Pretreatment *Proc. Soc Exptl Biol Med* 111 484 (1962)
21. BURN, J H, & RAND, M J The Action of Sympathomimetic Amines in Animals Treated with Reserpine *J Physiology* 144 314 (1958)
22. FLEMING, W W, & TRENDLENBURG, U. The Development of Supersensitivity to Norepinephrine after Pretreatment with Reserpine *J Pharmacol & Exper Therap* 133. 41 (1961)
23. KRAYER, O, ALPER, M H, & PAASONEN, M K Action of Guanethidine and Reserpine upon the Isolated Mammalian Heart. *J Pharmacol & Exper Therap* 135 164 (1962).
24. SMULYAN, H, MARKASON, C R, KEIGHLEY, J F, CUDDY, R P, EICH, R H, & LYONS, R H Effects of Reserpine on the Circulation and on the Circulatory Responses to Tilting and Norepinephrine *Am J Cardiol* 11. 743 (1963)
25. BRODIE, B Recent Views on Mechanisms for Lowering Sympathetic Tone *Circulation* 28 970 (1963)