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The Use of Propranolol in the Surgical Treatment of Thyrotoxic Patients

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BETA-ADRENERGIC STIMULATION produces many of the symptoms associated with hyperthyroidism. These include central nervous system hyperactivity, sweating, fever, dilation of blood vessels and increased rate and force of contraction of the heart. The knowledge of this established a rational plan for the use of beta-adrenergic blockade to alleviate the signs and symptoms of thyrotoxicosis.

Propranolol, a beta-adrenergic blocking agent, was introduced by Black.[1,2] Its effective use in controlling hyperthyroid manifestations and crisis was subsequently established.[3,4,6,8] Vinik and coworkers[9] found that Propranolol combined with iodine was an effective preparation for hyperthyroid patients undergoing thyroidectomy. In 1970, Pimstone and Joffe[5] reported the administration of Propranolol and iodine for 10 to 14 days was an ideal regimen to use in the preparation of their patients. They included in their studies several patients who were not benefited by long-term iodine therapy and were treated by Propranolol for only 3 to 4 days preoperatively without any untoward effects during operation. These reports suggested that Propranolol could be the sole drug to use in the preparation of hyperthyroid patient undergoing thyroidectomy and that iodine was unnecessary. The uniformly favorable response to Propranolol observed in 20 patients is the subject of this report.

Materials and Methods

Twenty patients with classic clinical and laboratory findings of hyperthyroidism consented to participate in this study. There were 13 women and seven men. The average age was 32 with the youngest being 16 and the oldest 56 years of age. Twelve patients were Caucasians, six Negro and two Oriental. No patient had undergone previous thyroid operation. Each patient was admitted to Georgetown University Hospital and observed for several days during diagnostic procedures. Vital signs were recorded frequently. Estimates of psychomotor activity, body warmth and perspiration were made. The presence or absence of eye signs were noted. Subjective evaluations were obtained regarding the patients state of inner agitation and sense of well being. Serum thyroxine levels were measured by displacement analysis with a normal range for T_4 (D) of 6.0–11.5 μg./100 ml. The T_4 levels averaged 20.1 μg./100 ml. with a range of 12.8 to greater than 25. Resin triiodothyronine uptake

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(RT_3U) was measured with a normal range of 26–35%. The T_3 uptake averaged 46.5% with a range of 26.9 to 56.8% ^{131}I thyroidal uptake were measured at 6 and/or 24 hours after a 5–50 microcurie oral dose of ^{131}I in the usual manner. The 6-hour average was 54.8% with a range of 35 to 86%. The 24-hour average was 64.2 with a range of 30 to 84%. Thyroid scans were done with ^{131}I or 99 m Technetium. Eighteen of the scans showed diffuse hyperthyroidism and two demonstrated nodules. Protein bound iodine determinations ranged from 8.4 to 25 ug/100 ml. with an average of 13.7 ug./100 ml. Plasma levels of Propranolol were measured in four patients before and after operation. These levels ranged from 35 to 200 ng./ml., consistent with the development of beta adrenergic blockade.[2] These specimens were iced immediately and spun down in a refrigerated centrifuge. The plasma was then separated and frozen at −20 C until determinations were carried out. The method utilized for the measurement of Propranolol was a modification of Black's *et al.*[2] developed in this laboratory. Propranolol was extracted into heptane-ethanol (99:1 v/v) from plasma, alkalinized with 0.1 N sodium hydroxide. The heptane extract was then reextracted with 0.1 N hydrochloric acid and Propranolol in the acid phase quantitated by fluorometry. The coefficient of variability in this method is 4% at low levels and 8% at higher levels of Propranolol.

No iodine or thionamides were used to prepare these patients. Nine patients had been treated previously with thionamides. However, none had been used in the 4 months prior to the institution of Propranolol preoperatively.

Oral Propranolol was administered every 3-6 hours with a total daily dosage ranging from 40–720 mg. No patient was operated upon who had undergone less than 4 days of treatment with Propranolol. The final preoperative dose was given orally, 1 or 2 hours before operation. No Propranolol was given or required during operation. Postoperatively the drug was reinstituted orally within 8 hours except in two patients who, because of nausea and vomiting, required small amounts of intravenous Propranolol. The drug was progressively decreased and then discontinued on the 4th to the 7th postoperative day.

Standard anesthetic technics were used with the exception that no atropine was given preoperatively. Induction was carried out with pentothal. The maintenance anesthesia consisted of either methoxyflurane and nitrous oxide, nitrous oxide, curare and morphine, or halothane and nitrous oxide.

Following operation frequent observations of the patients' vital signs and subjective symptoms were recorded. Serial determinations of thyroxine levels, ^{131}I thyroidal uptakes and scans were measured in each patient on the third to the 11th postoperative day, and after 3 and 6 months following operation.

Results

Within the first day of preoperative Propranolol therapy all patients achieved a normal or near normal metabolic level, although the measurable thyroid function was not influenced. The ^{131}I uptake, serum thyroxine level and protein bound iodine were not influenced by this drug despite the fact that all vital signs and symptoms consistent with metabolic stimulation were promptly abolished. Preoperatively there was no discernible increase in the size of the thyroid gland. In a few patients a slight reduction in the size of the gland occurred with a decreased bruit and thrill.

At the time of operation, the thyroid gland was resected without any technical difficulty, being less vascular and friable than in cases in which standard antithyroid drugs were employed preoperatively. Bilateral subtotal thyroidectomies were performed on all patients. Blood loss varied from 50 to 150 cc. There were no nerve injuries or evidence of parathyroprevia in these patients.

The postoperative disappearance time of elevated endogenous serum thyroxine was plotted as a semilogarithmic function, revealing a half-disappearance time of 7.2 days.

There were no significant anesthetic complications other than an occasional premature auricular contraction in some patients, and premature ventricular contractions in one patient. Three patients manifested bradycardia with halothane. All but one returned to a normal level when the amount of halothane was decreased; the remaining patient required 0.4 mg. of atropine intramuscularly. No variations in blood pressures were noted. There were no cases of overt thyroid storm in the perioperative period.

Postoperatively all patients remained in the hospital until Propranolol therapy was discontinued. This period varied from 4 to 7 days. At the cessation of medication, all patients maintained normal vital signs and were considered euthyroid. Although no patients have manifested any evidence of recurrence, the time of follow-up is considered too short to make a valid statement concerning this response.

Discussion

The mechanism by which beta-adrenergic blockade favorably modifies the clinical manifestations of thyroid hormone excess and the response to operation is not clear. So many of the signs and symptoms of thyrotoxicosis resemble the manifestations of catecholamine excess that the interrelationships of the thyroid hormone and the sympathetic nervous system have been the subject of investigation for many years. Reserpine and guanethidine cause depletion of body catecholamine stores and have been shown to improve the tremor,

sweating, palpitations, tachycardia and some of the eye signs of thyrotoxicosis. These drugs have therapeutic disadvantages because of a delay in clinical improvement and associated side effects. Propranolol, an adrenergic blocking agent, seems to be at present the drug of choice in the short-term definitive surgical treatment of patients with thyrotoxicosis.

Although one of the great advantages of Propranolol is its rapid action, it must be remembered that its effect following ingestion of the drug lasts only a matter of hours, thereby not affording the postoperative cushion to which we are accustomed with the use of thionamides and iodines. This became manifest when one patient, who was well-controlled prior to and during operation, inadvertently did not receive postoperative Propranolol. Fifteen hours after operation tachycardia developed and 2 hours later she manifested all signs and symptoms of approaching thyroid crisis. Five minutes after receiving 1.0 mg. of intravenous Propranolol there was a definite decrease in psychomotor activity with a concomitant fall in the pulse rate to a normal level. Forty milligrams of the drug was given orally and repeated 2 hours later with complete and prompt correction of the abnormal vital signs.

Atropine was not used as a preoperative medication to avoid tachycardia which may result from parasympathetic blockade in thyrotoxic patients. The use of the anesthetic agents, halothane and methoxyflurane, obviated the need for atropine since they do not stimulate tracheobronchial secretions, constrict bronchioles or cause laryngospasm. Both of these halogenated agents also aid in the control of the cardiac rate, halothane by a combined vagotonic effect and depression of sinoatrial and atrioventricular nodes, and methoxyflurane by a vagotonic action. With this anesthetic technic, intramuscular atropine in doses of 0.4 to 1.0 mg. can be reserved for elective use during operation, to correct any significant bradycardia that may develop that has not responded to a decrease in the concentration of the halogenated agents.

The amount of Propranolol to be given was largely determined by the clinical state and heart rate of each patient. The majority received 80 mg. every 6 hours or a total of 240 mg. per day. Two patients, not included in this series, could not be brought under control with Propranolol although they received 120 mg. every 6 hours plus an IV injection of 10 mg. Although there was symptomatic improvement, the pulse rate remained elevated. It was considered injudicious to operate on these patients at this time. Subsequently they were given large doses of thionamides in addition to Propranolol. Both underwent subtotal thyroidectomies a month after this treatment without any untoward operative or postoperative effects. The reason for the failure of Propranolol in these patients is unknown.

Propranolol does not affect thyroidal iodine accumulation. The data in this study and in an earlier report[3] demonstrates that serum thyroxine levels were unchanged by Propranolol. This afforded a unique opportunity to record the rate of decline of elevated thyroxine levels following subtotal thyroidectomy. Postoperatively there was a progressive downward trend, reaching a normal level about the seventh day in those who became euthyroid, while in those who subsequently became hypothyroid a further fall in the thyroid level occurred. This permitted us to identify with considerable accuracy those who would subsequently become hypothyroid. The endogenous thyroxine half disappearance time was 7.2 days in this group of 20 patients. The result is close to the 6.2 days reported by Sterling and Chodos,[6] as the biologic half life of ^{131}thyroxine in euthyroid individuals. It contrasts sharply with the T1/2 of 2.9 days for thyroxine in hyperthyroid patients reported by the same investigators, suggesting that Propranolol reduced the hypermetabolism if not the hyperthyroidism.

Summary

Propranolol is a valuable adjunct in the management of hyperthyroid patients. It allows the thyrotoxic patient to be prepared for operation more promptly than has heretofore been possible. It is the drug of choice in thyrotoxic patients who have proved to be intolerant or unresponsive to conventional antithyroid drug therapy. It does not interfere with the usual tests for hyperthroidism. It is the drug of choice for treatment and prevention of thyroid crisis. Since the drug is a beta-adrenergic blocking agent it does not decrease the circulating thyroxine. For this reason it should be continued for 4 to 7 days postoperatively. Iodine need not be combined with Propranolol in the preoperative preparation of the majority of thyrotoxic patients. While the number of patients in this report is small, the uniformity of responses is striking and so favorable that we have adopted the use of Propranolol as the drug of choice for the perioperative management of patients undergoing subtotal thyroidectomy in this institution.

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Discussion

Dr. Paul C. Kiernan (Washington, D. C.): Washington, and Georgetown University, are greatly privileged to have Dr. Coffey as a surgeon. His many contributions are well known to all of you. In part, this is due to his ability to stimulate and work closely with such individuals in the Medical Department as Drs. Canary and Mackin. His work in acute hyperparathyroidism, tumors of the pancreas and adrenal, have been in part due to this close association. One other of his assets, which is apparent to you, is his ability to select and train such attractive and well-qualified surgeons as Dr. Lee.

The lack of cushion and the quick ability to escape from the effect of Propranolol, I think, should not disturb us. Those of us who continue to be impressed with the efficacy of iodine in the preparation of patients with hyperthyroidism for surgery are pleased to have another agent which can so quickly prepare them.

The speedy control of the hypermetabolism with Propranolol allowing subtotal thyroidectomy to affect the desired surgical remission of the hyperthyroidism has great appeal.

I would like to ask about one group of patients, the asthmatic, and the use of Propranolol.

Dr. Benjamin F. Byrd, Jr. (Nashville): Dr. Coffey and Dr. Lee were kind enough to let me look over a copy of this paper, and there were two or three remarks that I thought the organization might benefit from in enlarging on their observations, and there are some questions I would like to ask—three questions and three observations, if I may.

One of the most interesting things is the fact that there were failures of preparation with Propranolol; and they were able to recognize these failures in preparation and to avoid the hazard of operating on the unprepared patient. The ability is present with this method of preparation to rapidly reduce the patient to a euthyroid state to avoid the dreaded complication of thyroid crisis in the postoperative period and to manage crisis when it did occur in one patient in their series, because of failure to take the drug. I think that the problems of operation which can be avoided with this technic are really remarkable.

I would like to ask them: Were their patients hospitalized throughout the entire administration of Propranolol?

I would like to ask just a little further about the reduction of vascularity and friability of the gland which was observed in the operating room, and I would have thought that these physical characteristics of the gland would have been more difficult to alter than a rapid 5 to 7-day period, and it is astonishing that without added iodine this was changed favorably.

Finally, do you expect any difference in the treatment of nodular and diffuse goiter?

I think that with this rapid preparation we may expect that the benefits of surgical treatment will be returned to common use, in view of the multiple complications of medical therapy, which are well known to us all through past experience.

Dr. Colin G. Thomas, Jr. (Chapel Hill): I, too, wish to compliment the authors on a very carefully performed and superb study, with respect to the effect of Propranolol in thyrotoxicosis and the role of this drug in surgical treatment.

Although thyrotoxicosis is thought to be dependent upon increased levels of thyroxin and triiodothyromine, many of the effects appear to be the augmented physiologic effects of cathecholamines. For example, the adrenergic receptors in the heart are strictly beta receptors. Thus the increased heart rate, cardiac output, and ventricular stroke work may be mediated by cathecholamines rather than the direct action of thyroid hormones.

It, thus, becomes logical to treat the symptoms of thyrotoxicosis by agents which interfere with catecholamines; namely, via beta adrenergic blockade.

The authors have emphasized that, using this method, one must rely completely upon clinical criteria for adequacy of control. At the same time, we should all realize that this drug does compromise normal homeostatic mechanisms. Those responses which may follow stress or shock may no longer appear. With the use of this drug we have to have careful monitoring, both in the pre- and postoperative period. Although intraoperative complications are rare with surgical treatment, nevertheless, they do occur.

For these reasons, we have elected to use the drug not as a sole means of preparation, but as an adjunct to standard methods of preparation with antithyroid drugs. It has been particularly useful in the following groups of patients: (1) the patients who have had toxic reactions to Tapazole or propylthiouracil; (2) those individuals in whom large doses have been required to control the disease—for example, over 800 mg. of propylthiouracil; (3) patients who are unreliable and uncooperative, and have not taken their antithyroid drugs. This is particularly true of some of the children; and (4) the pregnant patient, in whom doses of antithyroid drugs are undesirable because of their ability to cross the placental barrier and perhaps affect the fetus.

Another indication which would certainly be reasonable would be the patient who was thyrotoxic and who required an unrelated operative procedure. It would seem to me this would be an ideal approach under these circumstances.

For most surgeons, I believe a reasonable course of therapy would be to utilize this drug as an adjunct to present methods and allow individuals with the competence of the authors to continue their studies to identify the over-all usefulness of this drug in the management of patients with thyrotoxicosis.

One of their points was the decreased cost of this approach. However, I note that the over-all length of hospitalization was approximately 11 to 12 days, whereas with other means of preparation this is usually between 4 and 6 days.

I have two questions: What would they consider the contraindications to the use of the drug, other than those patients who do not respond? I have in mind in particular individuals who have thyrocardiac disease. Secondly, it seemed from their observations that the incidence of hypothyroidism might be somewhat higher in this patient group. Have they compared their incidence of hypothyroidism in patients treated this way with those managed by more standard methods of preparation?

Dr. Charles Wray (Augusta): Dr. Thomas has reviewed the manner in which we have thought about the use of this drug. I would like to mention that we are indebted to Dr. Raymond Alquist, who is Professor of Pharmacology at the Medical College of Georgia, for the development of the concepts of alpha and beta