IODOTHIOURACIL IN TREATMENT OF TOXIC GOITRE

BY

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In 1948 Barrett, Goodman, and Dittmer synthesized several organic combinations of halogens with thiouracil, of which 5-iodo-2-thiouracil proved most suitable for clinical trial. Because of the avidity of the hyperthyroid gland for iodine, the concentration of thiouracil in the gland might be expected to be greater after administration of iodothiouracil than after an equivalent dose of uniodinated thiouracil; a lower dosage could then be used, and the frequency of toxic effects would thus be reduced. It was also thought that the concurrent administration of iodine might diminish the hyperplasia and vascularity of the thyroid gland otherwise induced by the thiouracil; a reduction in the duration of pre-operative treatment would thus be possible and the technical difficulties of excision would be minimized.

Animal Experiments.—Experiments on rats and chicks have shown that the reduction in metabolism produced by iodothiouracil was quantitatively the same as that produced by thiouracil with or without the concurrent administration of potassium iodide (Barrett and Gassner, 1951). The thyroid histology of animals treated with iodothiouracil resembled the normal more closely than did that of animals treated with iodide and thiouracil singly or in combination (Barrett, Gassner, and Dittmer, 1951). Gassner *et al.* (1950) have also shown that iodothiouracil was less goitrogenic than thiouracil with and without iodide, and that it inhibited the goitrogenic action of exogenous thyrotrophic hormone, whereas thiouracil, alone or with iodide, augmented it.

Previous Clinical Trials

Reports on the use of this drug in over 190 patients have already been made from North America (Williams *et al.*, 1949; McClintock and Lyons, 1951; Catz *et al.*, 1951; Goldner and Kirschenfeld, 1952; Catz and Starr, 1953). The initial daily dosage varied from 50 to 800 mg., the optimum dosage appearing to lie between 200 and 400 mg., and the maximum clinical response was obtained in from eight to twenty-two days. Most workers found that some patients responded poorly; McClintock and Lyons (1951) believed that full remission was rarely produced. Definitive long-term therapy with iodothiouracil did not appear to be satisfactory owing to the incomplete and erratic control which was obtained; therefore the drug was mainly used in the preparation of patients for subtotal thyroidectomy. All these reports agree that the results obtained were from the surgical point of view satisfactory, the gland being less friable and vascular than after the usual preparation with a thiouracil derivative and iodine. Histologically, the glands appeared to be well involuted, and Catz and Starr (1952)

reported that "in hyperthyroid patients prepared for operation with iodothiouracil, the thyroid epithelium has a lower average mean acinar cell height than in all the other treatment groups," which included groups treated with iodine alone and with iodine and a thiouracil drug together; in other words, the histology most closely resembled that of the normal gland in the group treated with iodothiouracil.

Present Investigation

Twenty-three patients with hyperthyroidism have been treated with sodium iodothiouracil ("itrumil"), 100 mg. of the drug containing 46 mg. each of iodine and thiouracil and 8 mg. of sodium. Eighteen patients were subsequently treated by subtotal thyroidectomy. The first seven patients were given 200 mg. of iodothiouracil daily, but as the condition of the glands at thyroidectomy was not so consistently satisfactory as had been expected the remaining patients were given 300 mg. daily. All patients were admitted to hospital and observed for seven to fourteen days before starting drug therapy; during this period of observation the diagnosis was confirmed clinically, by radio-iodine studies and by estimations of the basal metabolic rate (B.M.R.). The latter test was repeated on three successive mornings, the lowest of the three readings providing a more accurate indication of the level of thyroid activity than a single reading. During the periods of observation and treatment the pulse rate (including the 'sleeping rate') was noted, the patients were weighed twice weekly, and exophthalmometer readings, measurements of neck circumference, and white blood cell counts were made weekly.

A further group of six hyperthyroid patients admitted thereafter for preparation for subtotal thyroidectomy was observed in a similar way and was treated with methylthiouracil and potassium iodide concurrently in daily doses equivalent to those of the thiouracil and iodine in 300 mg. of iodothiouracil.

Clinical Effects

In most patients, between the third and eighth days of treatment, and usually on the fifth day, a change in the pattern of the pulse chart could be noted, the lowest pulse rate of the day (often the sleeping pulse rate) having fallen by about 10 beats, and the daily range of the pulse rate being also reduced, although to a less extent. This change commonly coincided with an improvement in the general condition of the patient and accompanied, or immediately preceded, an increase in weight. In almost all cases the increase in weight continued until the end of the three weeks' treatment which preceded operation or discharge from hospital. A further fall in the pulse rate was not so common, and in many cases the lowest level and the range of the daily pulse rate rose slightly towards the end of this period of observation; this phenomenon was probably associated with the increase in the patient's physical activity, which was encouraged before operation or discharge, although it may represent an escape from control by the antithyroid drug.

All but one of these patients gained weight during treatment with iodothiouracil, and during the first three weeks of treatment the average daily gain in weight was 5 oz. (140 g.), the gain being higher in those with diffuse goitre than in those with nodular goitre, and higher in those given 300 mg. of iodothiouracil daily than in those given 200 mg. daily.

Estimations of the B.M.R. provide a less reliable means of assessing progress, owing to the difficulty of producing a basal state in hyperthyroid patients. The average daily fall in B.M.R. during the first three weeks of treatment was about 1.5%, and again the average daily fall was greater in the patients with diffuse goitre than in those with nodular goitre, and greater in those treated with 300 mg. of iodothiouracil daily than in those treated with 200 mg. daily.

In none of the six patients treated for two months or more did an increase in the size of the goitre become obvious. Increase in exophthalmos did not occur during treatment in

any patient, but in two, following thyroidectomy, there was a temporary increase of 2 to 3 mm. accompanied by slight ocular discomfort. A transient maculo-papular rash developed in one patient, but disappeared without treatment being stopped. Agranulocytosis, leucopenia, or any other toxic effect was not observed.

Surgical and Histological Findings

All thyroidectomies performed on these patients were done by one surgical team. The surgeon was of the opinion that the glands of patients prepared for operation with iodothiouracil were firmer, less vascular, and less friable than the glands of patients who receive the usual preparation of a thiouracil drug followed by iodine. Particularly was there a reduction in the size of the surface veins of the gland, though periglandular adhesions seemed more dense. In half of the patients the condition of the gland was comparable to that found after preparation with iodine alone. The post-operative course in no case caused anxiety, and was usually uneventful.

Although in four of the seven patients treated with 200 mg. of iodothiouracil daily ideal technical conditions were found at thyroidectomy, in the others the results were not so satisfactory—the gland in one patient who received 200 mg. daily for only twelve days being as vascular and friable as the glands found in patients treated with thiouracil without iodine. It was on this account that the daily dose of iodothiouracil was increased to 300 mg.

Evidence of involution, with good colloid content, was found in most of the excised goitres. In two-thirds of the cases there was, however, some degree of hyperplasia, which was never extreme and was usually slight or moderate. In the remaining third the epithelial cells were cuboidal or flattened (Table I).

TABLE I.—Summary of 18 Cases of Toxic Goitre Prepared for Surgery with Iodothiouracil

Case No.	Age and Sex	Goitre	Lowest B.M.R. before Treatment	Iodothiouracil		Surgeon's Impression*	Histological Evidence of Hyperplasia
				Daily Dose	Duration in Days		
1	38 F	D	+16%	200 mg.	24	A	None
2	34 F	D	+54%	200 "	17	A	"
3	46 F	N	+68%	200 "	12	C	Moderate
4	33 F	D	+45%	200 "	23	B	Marked
5	30 F	D	+53%	200 "	25	A	"
6	34 F	D	+80%	200 "	30	A	None
7	53 F	D	+50%	200 "	27	B	Slight
8	47 F	N	+26%	300 "	22	A	Marked
9	51 M	D	"	300 "	60	A	None
10	28 F	D	+54%	300 "	25	B	Moderate
11	48 M	D	+50%	300 "	30	A	Slight
12	37 F	D	+46%	300 "	23	A	"
13	55 F	N	+34%	300 "	23	B	"
14	42 M	D	+48%	300 "	19	A	"
15	46 F	D	+34%	300 "	19	B	Moderate
16	48 F	N	+17%	300 "	20	B	None
17	48 F	N	+55%	300 "	18	B	"
18	50 F	D	+56%	300 "	18	B	Moderate

D=Diffuse. N=Nodular.

* Classification of surgeon's impression of condition of thyroid gland: A=comparable with glands after preparation with iodine alone; B=comparable with the more satisfactory glands after preparation with thiouracil followed by iodine; C=unsatisfactory—excessive vascularity and friability.

Long-term Treatment

One patient with hyperthyroidism complicated by auricular fibrillation and congestive heart failure was treated with 300 mg. of iodothiouracil daily for 60 days, during which time clinical improvement was continuous; at operation the condition of the thyroid gland was ideal, there being little increase in vascularity and no increase in friability or periglandular adhesions. Five patients have been treated with iodothiouracil for four months or more; in one patient with mild hyperthyroidism and exophthalmic ophthalmoplegia, although treatment was continued for nine months, good control of the hyperthyroidism was maintained, decrease in exophthalmos occurred, and there has been no relapse in the three months since treatment was stopped. In the four other patients who have been treated for from four to seven

months control has not been so satisfactory, and iodothiouracil has been replaced, with benefit, by methylthiouracil in two patients.

Comparison with Patients Treated with Methylthiouracil and Iodine

The average daily gain in weight and the fall in B.M.R. were identical in the group of patients treated with equivalent doses of iodothiouracil and iodine. The condition of the thyroid at operation, from the point of view of vascularity and technical difficulty, was a little less satisfactory in the latter than in the iodothiouracil group, and histological evidence of hyperplasia was more frequent and more obvious (Table II).

TABLE II.—Summary of Six Cases of Toxic Goitre Prepared for Surgery with Methylthiouracil and Potassium Iodide Concurrently, in Dosage Equivalent to 300 mg. Iodothiouracil Daily

Case No.	Age and Sex	Goitre	Lowest B.M.R. before Treatment	Duration of Treatment in Days	Surgeon's Impression*	Histological Evidence of Hyperplasia
19	46 F	D	+28%	19	B	Moderate
20	39 F	N	+50%	25	C	"
21	39 F	D	+26%	28	A	None
22	34 F	D	+10%	16	B	Moderate
23	33 F	D	+50%	22	B	"
24	58 F	N	+26%	20	C	"

* See footnote to Table I.

Discussion

In our experience iodothiouracil in daily dosage of 300 mg. for at least 17 days is a very satisfactory preparation for thyroidectomy in hyperthyroidism. A definite improvement in the clinical state occurs within a week of the start of treatment, there being thereafter a steady rise in weight of over 2 lb. (0.9 kg.) a week and a fall in B.M.R. of about 1.5% daily. The majority of patients are therefore fit for surgery within four weeks of starting iodothiouracil, and the field provided for the surgeon is technically satisfactory. It is thus possible to give all patients the advantage of an anti-thyroid agent in preparation without increasing the difficulties of the subsequent operation and without increasing appreciably the period of incapacity.

It is not so certain, however, that iodothiouracil possesses any new or distinctive features as a drug for the specific treatment of hyperthyroidism. The early clinical response, the tendency to escape from control after two to three weeks' treatment, and the difficulty in maintaining control in long-term treatment are suggestive of an iodine action, and it has yet to be shown that the iodine and thiouracil fractions of iodothiouracil act in the body in the organically combined form. It has been suggested that the studies of Plummer (1950) on the urinary excretion of the iodothiouracil are in favour of such an action, but the implications of these findings are doubtful.

Comparing the results of iodothiouracil treatment with those of methylthiouracil and iodine, we have been unable to show any significant difference beyond the impression that in the iodothiouracil group the operative field showed less excessive vascularity and the histological appearance was more commonly that of complete involution. Catz and Starr (1953), however, found that a shorter period of treatment was necessary to control hyperthyroidism with iodothiouracil than with thiouracil and iodine, that increase in goitre size occurred in the majority of patients treated with thiouracil and iodine but in none of those treated with iodothiouracil, and that the mean acinar cell height was lower in those treated with iodothiouracil, this signifying greater involution.

Astwood (1944) suggested that the actions of iodine and thiouracil in hyperthyroidism might be antagonistic, and that these drugs should therefore not be given simultaneously; it is in fact common practice in this country, when preparing

hyperthyroid patients for surgery, to discontinue the thiouracil two to three weeks before operation and to administer iodine alone for the remaining period (Rundle, 1951; Lange, 1953). However, Maxwell *et al.* (1946) and Williams (1946) reported satisfactory results with the concurrent administration of thiouracil and iodine. Rawson *et al.* (1945) believed that the iodinating and involuting actions of iodine are separate, and that, although the administration of the iodine does not result in the synthesis of thyroid hormone when iodine and thiouracil are given together, it does cause involution of the gland.

Conclusion

Although the number of cases observed in the present series is small we believe that the use of concurrent thiouracil and iodine (whether given as iodothiouracil or as methylthiouracil with potassium iodide) is a most satisfactory method of preparing for operation patients with moderate or severe hyperthyroidism. Those patients with mild hyperthyroidism who require operation are adequately prepared with iodine alone. Preparation with concurrent thiouracil and iodine is more rapid and produces a more satisfactory surgical field than does preparation with thiouracil followed by iodine. In cases of moderate severity the relatively slight increase in the duration of pre-operative treatment, compared with the duration of pre-operative treatment with iodine alone, is fully justified by the increased degree of safety obtained.

Summary

The literature concerning iodothiouracil, an organic combination of iodine with thiouracil, is reviewed, and a further clinical trial of this drug is reported.

Twenty-three patients suffering from hyperthyroidism, 18 of whom had subsequent thyroidectomies, were treated with iodothiouracil in doses of 200 to 300 mg. daily for periods of 12 days to 7 months.

The reduction in hyperthyroidism and the involution produced in the thyroid gland of patients prepared for surgery were most satisfactory; the results of prolonged medical treatment with iodothiouracil were variable.

It is doubtful whether the pharmacological properties of iodothiouracil differ from those of the constituent iodine and thiouracil fractions when the latter are administered at the same time.

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The National Gastroenterological Association announces that the name of its official publication, established in 1934, has been changed from *The Review of Gastroenterology* to *The American Journal of Gastroenterology*. There has been no change in the editorship. An earlier journal of this name was published from 1911 to 1914 by the American Hospital for Diseases of the Stomach, Philadelphia.

LONG-TERM THERAPY OF THYROTOXICOSIS WITH THIOURACIL COMPOUNDS

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Now that the treatment of thyrotoxicosis by thiouracil compounds has been in use for a number of years, it is becoming possible to determine its long-term effects and, in particular, the conditions under which this therapy is likely to be most successful. Most of the earlier contributions to this aspect of the subject have been reviewed by Astwood (1949), and accounts of more recent investigations have been published by Himsworth (1948), Williams (1949), Dunlop and Rolland (1950), Trotter (1950), Poate (1950), Wing and Asper (1952), and Douglas and Kennie (1952).

The present report is a summary of observations which began in 1944 at the Sheffield Royal Infirmary on the effects of treating thyrotoxicosis by means of thiouracil compounds. The inquiry was planned with a view to throwing light on three main questions which are of special interest to the medical practitioner: (a) How successful are these drugs in initially controlling the signs and symptoms of this disease? (b) To what extent can control be maintained over long periods by continuous administration of maintenance doses of the drug? (c) What are the chances of relapse after maintenance treatment is withdrawn? In particular, is length of remission after withdrawal related to such factors as the age of the patient, length of his illness, and the duration of his treatment before withdrawal?

Procedure

A total of 126 patients with typical signs and symptoms of thyrotoxicosis were treated for varying periods of up to six years with thiouracil, methylthiouracil, or propylthiouracil, according to the scheme already described in previous communications (Wilson, 1946; Wilson and Goodwin, 1947). As was pointed out previously, we have found that, though propylthiouracil was not superior to methylthiouracil, both compounds were less apt than thiouracil to produce toxic effects, and that the therapeutic response was favourable in either type of thyrotoxicosis. For the purpose of the present analysis no attempt is made to distinguish patients with primary from those with secondary thyrotoxicosis, or to differentiate between them according to severity of the disease, presence or absence of specific symptoms, the particular thiouracil compound and dose used, and the length of treatment needed before initial control was achieved. "Initial control" was assessed by the criteria previously described (Wilson, 1946). All patients who were controlled initially were given maintenance treatment, and from 94 of these it was subsequently withdrawn

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