Antithyroid treatment: a personal series

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Introduction

Since the introduction of thiouracil in 1943 antithyroid treatment for thyrotoxicosis has increased widely and has proved safer and more effective in carefully selected cases as the years have passed. Since 1951 carbimazole has been highly favoured in this country, being considered the least toxic agent in large-scale surveys (Burrell, Fraser & Doniach, 1956). Later (Willcox, 1962), it was shown that, with careful personal selection of suitable cases and with personal dosage control, fifty-three (64%) of eighty-three cases were successfully treated, without relapsing, with methyl thiouracil and fifty-five (82%) of sixty-seven cases with carbimazole. Fifty-eight per cent of this group had been followed up for 5 years or longer. The relapse rate in the two groups was 22% and 9% respectively, a relapse being defined as recurrence of toxic features occurring more than 6 months after completion of a course of treatment. The duration of treatment aimed at was 1 year but in cases in which loss of weight and other symptoms quickly recurred following withdrawal of the drug, treatment was necessarily continued for variable periods, as long as 2 years in a few cases.

The present follow-up study is an analysis of all cases personally selected for treatment from cases sent for consultation from 1948 until December 1965. In the early period, 1948-53, methyl thiouracil was used and since 1953 carbimazole alone.

Selection of cases

In selecting suitable cases for long-term treatment the co-operation of surgical colleagues has been maintained. They have invariably carried out partial thyroidectomy in cases referred to them and they have themselves referred patients both for long-term antithyroid treatment and sometimes for preoperative control of toxic features.

Patients selected were preferably those with obvious toxic features, with soft diffuse enlargement of the thyroid of moderate or small size who were not distressed by the appearance of the neck

or pressure symptoms. Though not all cases attained such standards, large unsightly goitres, especially those with hard nodules, were rejected. Where diagnosis was in doubt radioactive iodine tests were carried out and in a few cases BMR estimations and sleeping pulse rates were carried out in hospital. With very few exceptions patients were treated throughout as out-patients and were not admitted except for heart failure or other reasons, though in a few cases diagnosis was made in patients admitted to hospital from other sources. During treatment patients were advised to lead a normal active life at household duties or other occupations, periods of rest being advised only exceptionally. Occasionally patients have refused operation, for a number of different reasons. In one case, who had had a partial thyroidectomy 21 years previously, further operation was refused in 1948. She was successfully treated and avoided surgery. Another patient with a cystic goitre of considerable size repeatedly refused operation over a period of 11 years during which she was sufficiently controlled to lead a normal life and was supervised through a successful pregnancy. Successful partial thyroidectomy was finally carried out.

Dosage

The routine period of treatment of 1 year was adopted in 1952 in view of the current opinion of those who had made extensive studies of thiouracil up to that time (Douglas & Kennie, 1952; Williams, 1950). Moreover, theoretical considerations of the action of antithyroid drugs on the production of hormone in the gland would support the idea of the need for treatment over a long period. The aim has been to administer the full dosage in tablet form in three divided daily doses for the first 2 months, the maximal daily dosage of carbimazole being 45 mg and of methyl thiouracil 600 mg; thereafter gradually reducing in stages to the minimal dosage effectively controlling toxic features, bearing in mind body weights, the resting heart rate and symptomatic improvement on the lines suggested by Riddell

(1956). Special awareness of the risks of incipient hypothyroidism and increasing enlargement of the thyroid is necessary so that treatment can be stopped and postponed until hormone balance is regained. Sometimes prolongation of the course is necessary for this reason or for the immediate return of symptoms, particularly weight loss, after termination of treatment. Experience has shown the variations in sensitivity to the drug and dosage requirements from case to case so that no routine dosage is recommended for all cases, the sex, stature and severity being factors to be considered. For this reason patients are kept under monthly observation for the first 6 months and thereafter are seen at least as often as 2 monthly. It is important that personal supervision be exercised by one doctor conversant with the aim of treatment (Riddell, 1963; Willcox, 1962) in order to avoid drug toxicity and overdosage. In many cases dosage has been on the lines set out in Table 1 though it is not suggested that this routine should be adhered to.

TABLE 1

Period (months)	Methyl thiouracil	Carbimazole
0-2	200 mg t.d.s.	10 mg t.d.s.
2-4	200 mg b.d.	10 mg b.d.
4-6	100 mg t.d.s.	5 mg t.d.s.
6-10	100 mg b.d.	5 mg b.d.
10-18	100 mg daily	5 mg daily

Assessment of results

The classification of all cases seen and the results of cases treated with long-term antithyroid drugs between 1948 and the end of 1965 is shown in Table 2. Relapse is defined as thyrotoxicosis recurring later than 6 months after completion of a course because it is considered that in cases in which early relapses occur treatment has been given over too short a period.

TABLE 2

Group	Thyrotoxicosis (1948-65)	No.	%
A	Complete remission without relapse	140	74
B	Relapsing later than 6 months after termination of a course	31	16
C	Treatment failed—referred for surgery	19	10
A, B and C	Total cases on long-term treatment	190	100
D	Referred for surgery initially	43	
E	Association with pregnancy	12	
F	Treatment incomplete at December 1965	44	
Total		289	

All cases in Groups A, B and C have been under observation for 1 year or more since completion of a course of treatment.

TABLE 3
Age groups and sex groups A, B and C

	Age (years)						Total
	10-19	20-39	30-39	40-49	50-59	60 onwards	
Female	4	23	43	42	26	20	158
Male	0	5	2	5	14	6	32
Total	4	28	45	47	40	26	190

Groups A and B

Table 4 illustrates the improved results with carbimazole compared with thiouracil. The decreasing proportion of relapses and failures in recent years may be explained partially by increasing personal experience in selection of cases and the use of carbimazole only since 1953.

TABLE 4

Comparison of methyl thiouracil and carbimazole, 1948-65 (Percentage relapse rate)

Group	Thiouracil (1948-62)	%	Carbimazole (1953-65)	%	Both	Total
A	53	65	85	79	2	140
B	18	22	13	12		31
C	10	13	9	9		19
Total	81	100	107	100		190

Of 140 cases in Group A, eighty-nine (63%) have been under observation for over 5 years and forty-three (31%) for over 10 years; in group B twenty-nine of thirty-one cases for over 5 years and nineteen (61%) for over 10 years. The completed years of observation of these patients are shown in Table 5.

TABLE 5

Group	Completed years of observation												Total
	12 or over	11	10	9	8	7	6	5	4	3	2	1-2	
A	31	5	7	8	12	9	6	11	22	17	6	6	140
B	17	1	1	4	3	1	1	1	1	1	0	0	31

Relapses. The relapse incidence was found to have no correlation with the duration of the course of treatment, being more dependent on causative factors in the individual, usually chronic mental strain, anxiety, overwork, occupational factors and intercurrent ill-health. It has sometimes been stated that relapse is a serious indictment of antithyroid therapy. That this is by no means true is shown by the good response of a second or third course of treatment even over a shorter period than before. There has been no difficulty in controlling relapses in this series. In one case relapse coincided with the onset of diabetes after a period of 5 years' observation and surgical treatment was accordingly carried out.

Group C

Treatment was abandoned in favour of surgery for the following reasons:

Increasing enlargement of thyroid (six carbimazole, six thiouracil)	12 cases
Increasing size and pressure symptoms (one carbimazole, one thiouracil)	2 cases
Poor response (thiouracil)	2 cases
Drug toxicity (thiouracil)	2 cases
Increasing size and toxicity (carbimazole)	1 case

Drug toxicity

No case of agranulocytosis was seen. In only six cases were serious toxic features encountered and in no case was carbimazole responsible. In two thiouracil-treated cases treatment was abandoned in favour of surgery. In one case recurrent keratitis and conjunctivitis was caused by thiouracil and in the other an eczematous rash and leucopenia. In four cases temporary leucopenia was associated with intercurrent infection. All patients were warned to omit treatment during the course of any such infection.

Deaths

There have been ten deaths among 192 cases during the follow-up period and in no case could death be attributed to the effects of antithyroid drugs. In one male patient, aged 31, sudden death occurred for which no cause was found post-mortem save an enlarged thymus. The details of these deaths are shown in Table 6.

TABLE 6

Cause of death	Age at death	Year of death	Treatment terminated
Cor pulmonale	72	1959	1956
Congestive heart failure	54	1964	1950
Congestive heart failure	64	1953	1950
Congestive heart failure	78	Nov. 1965	Sept. 1965
Malignant hypertension	53	1959	During course
Cerebral haemorrhage and hypertension	67	1950	6 months before death
Recurrent cardiac infarction	65	1959	2 months before death
Cerebral apoplexy	70	1962	1952
Aortic stenosis and heart failure	76	1965	1961
Sudden death, enlarged thymus	31	1962	1960

Association with pregnancy

Antithyroid treatment is the treatment of choice during pregnancy. In no case was operation indicated in twelve cases supervised. Six cases became pregnant during courses of carbimazole (five) and methyl thiouracil (one) and in every case treatment was completed 1 month or earlier before full term. In six cases (three methyl

thiouracil, three carbimazole) treatment was started during pregnancy, in the 2nd month (two), 3rd month (two) and 5th month (two). One of these mothers was delivered of a macerated foetus due to Rh antibodies in the mother in 1954. The foetal thyroid was microscopically normal. The remaining babies were healthy and progress satisfactory. Treatment of the mothers was terminated or interrupted 1 month before the expected date of delivery in order to avoid the possible secretion of drugs in the mother's milk (Illingworth, 1953).

Discussion

There is no doubt that partial thyroidectomy is the treatment of choice for thyrotoxicosis associated with large toxic goitres, for those with pressure symptoms or large unsightly goitres, and for the few who fail to respond satisfactorily to antithyroid drugs.

Early experience with thiouracil and allied compounds showed that permanent remission of toxic symptoms was attainable in 65% of cases and since 1953 the use of carbimazole has improved this expectation of success to nearly 80%, though so far only thirty-five of eighty-five cases (41%) have been under observation for over 5 years. These results indicate that carbimazole is more effective than methyl thiouracil though more careful selection of cases in recent years may play a part in achieving this improvement.

Study of cases in which treatment had to be abandoned showed that in most cases the thyroid became larger with or without pressure symptoms—changes which are reversible if the drug is withdrawn. This is much more likely to occur in initially large or nodular goitres of long standing whereas diffuse, soft goitres of recent origin may become smaller during treatment on minimal effective dosage, moreover toxicity is more easily and quickly controlled and prolongation of the course over 1 year is less often required (Pulver & Brundler, 1957). Since 1962, therefore, close attention has been paid to careful personal selection of cases. The pitfalls of antithyroid therapy are threefold; overdosage may lead either to further enlargement of the thyroid or to insidious hypothyroidism. Early recognition and drug withdrawal usually allows hormone balance to be restored and the gland to subside. Thirdly, leucopenia may be prevented provided the drug is withdrawn during acute infections.

For these reasons it is advocated that, following maximal dosage (45 mg of carbimazole daily) for 1 or 2 months, gradual reduction to minimal effective dosage is the aim to be attained. In a few cases immediate relapse occurs following termination of the course at the end of 1 year, necessitat-

ing prolongation of the course to 1½ or 2 years; especially is this likely when chronic stress factors persist. Such factors are likewise found in cases which relapse later on. These relapses are just as easily treatable, there being no loss of sensitivity to further administration of the drug.

Antithyroid treatment with carbimazole at the present time is the treatment of choice in pregnancy and is of great value in thyrotoxic heart failure, in patients refusing operation or relapsing after it, and in pre-operative control before partial thyroidectomy.

In a recent review of the treatment of thyrotoxicosis Hershman (1966) stresses the value of antithyroid drugs in pregnancy, young patients and cases of recent onset. In a study of the work of nine writers from 1953 to 1964 incidences of remission varied between 45% and 72%, the minimum follow-up period being 4 years. Using this standard of assessment, the results in this series show an incidence of 69% of remissions after 4 years, and in the writer's earlier paper (Willcox, 1962)—64%.

Summary

A long-term follow-up study has been made of antithyroid treatment in 190 cases of thyrotoxicosis using methyl thiouracil and carbimazole from 1948 to the end of 1965. One hundred and forty cases (74%) have had complete remissions, without so far relapsing, and eighty-nine (63%) of these patients have been observed for over 5 years. Thirty-one cases (16%) have so far relapsed and there has been no difficulty in controlling relapses.

Carbimazole was found to be more effective and less toxic than methyl thiouracil. Eighty-five of 107 patients treated with this drug responded very

satisfactorily without relapsing, of whom thirty-five (41%) have so far been under observation for over 5 years. Thirteen cases (12%) have relapsed and in nine (8%) treatment had to be abandoned in favour of surgical treatment.

It is believed that success can best be achieved by careful selection and personal supervision of suitable patients and by minimal effective maintenance dosage over a period of at least 18 months or even longer in a few cases.

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