EFFECT OF D-THYROXINE ON THYROTOXICOSIS AND ON THE ASSOCIATED EXOPHTHALMOS

BY

W. D. ALEXANDER, M.B., F.R.F.P.S.
M.R.C.P.Ed.

D. A. KOUTRAS, M.D.

W. W. BUCHANAN, M.B., F.R.F.P.S.
M.R.C.P.Ed.

AND

J. CROOKS, M.D., F.R.F.P.S., M.R.C.P.
M.R.C.P.Ed.

From the University Department of Medicine,
Gardiner Institute, Western Infirmary, Glasgow

D-Thyroxine, the optical isomer of the naturally occurring L-thyroxine, has aroused considerable interest because of the reported dissociation of its calorogenic effect from its other effects (Boyd and Oliver, 1960). A marked decrease of the radioiodine uptake by the thyroid has been observed after administration of D-thyroxine (Starr and Liebhold-Schueck, 1953). In some thyrotoxic patients treated with D-thyroxine Greene and Farran (1958) observed a fall in thyroid radioiodine uptake accompanied by a remission of symptoms, which they attributed to a decreased production of thyroid-stimulating hormone. If D-thyroxine can be shown to be effective in the treatment of thyrotoxicosis it would have advantages over antithyroid drugs at present in use, since it would be a more rational form of treatment and, moreover, should not give rise to sensitivity reactions.

In order to assess the possible value of D-thyroxine in the treatment of thyrotoxicosis, we have followed the clinical progress of patients given this drug, using the therapeutic index devised by Crooks *et al.* (1960). We have also treated a small group of thyrotoxic patients with iodine in amounts equivalent to that contained in the doses of D-thyroxine. Estimations of the absolute iodine uptake (A.I.U.) in $\mu\text{g.}$ of stable iodine per hour were carried out in order to determine whether any reduction in radioiodine uptake (% of dose) by the thyroid reflected a diminution in the uptake of stable iodine. Reduction in radioiodine uptake is not necessarily accompanied by a reduction in absolute iodine uptake. Dissociation could arise from an increase in the total amount of circulating iodine which would cause a relative reduction in the proportion of radioactive atoms. Thus the number of radioactive atoms taken up by the thyroid may be diminished, while the number of stable iodine atoms may remain the same or even increase.

A further group of patients were treated with a combination of D-thyroxine and methylthiouracil, and the changes in the degree of exophthalmos were compared with a similar group of patients treated with methylthiouracil alone.

Materials and Methods

Four groups of thyrotoxic patients were studied. In each case the diagnosis was made on clinical grounds (Crooks *et al.*, 1959) and confirmed by both P.B.I. determinations (Farrell and Richmond, 1961) and radioiodine studies. Group 1 consisted of eight patients treated with D-thyroxine—three with 1 mg. and five with 4 mg.

daily. Every two weeks measurements were made of body weight, therapeutic index (Crooks *et al.*, 1960), and the 2½-hour thyroid uptake of I-132. In three of these patients studies of stable iodine metabolism were carried out (Koutras *et al.*, 1960) before and after 12 weeks of treatment with 4 mg. of D-thyroxine daily. A control group of six thyrotoxic patients (group 2) were treated with equivalent amounts of potassium iodide (3.32 mg. of KI $\approx$ 4 mg. of D-thyroxine), and estimations of A.I.U. were made before and at the end of 12 weeks of treatment. The A.I.U. is calculated as the product of the plasma inorganic iodine (P.I.I.) and the thyroid iodine clearance rate. The P.I.I. was estimated from measurements of the specific activity of the urinary iodine (Koutras *et al.*, 1960). Group 3 consisted of seven thyrotoxic patients treated with methylthiouracil 600 mg. daily for two weeks, followed by 300 mg. daily until euthyroid. Throughout the study these patients received 4 mg. of D-thyroxine daily. Every two weeks the therapeutic index and body weight were recorded and exophthalmometry was carried out (Zeiss-Hertel). Twelve thyrotoxic patients treated with methylthiouracil alone in the same doses acted as a control group (group 4).

Results

Group 1 (D-Thyroxine) and Group 2 (Potassium Iodide)

The results are shown in the Chart. The I-132 uptakes are shown separately for each dosage of D-thyroxine.

Response to D-thyroxine in eight thyrotoxic patients.

whereas therapeutic indices and body weight are shown together since neither dosage produced any significant change. The thyroid radioiodine uptake after 12 weeks of treatment decreased by a mean of 34% of the dose in those patients treated with 4 mg. daily. In those treated with 1 mg. daily the decrease was only 15%. The fall in uptake (49% at 12 weeks) was of greater magnitude and occurred more rapidly in the six cases treated with potassium iodide in amounts equivalent to 4 mg. of D-thyroxine (group 2). In contrast to the decreased radioiodine uptake, the stable iodine studies (Table I) showed that D-thyroxine caused no depression in the iodide-trapping mechanism of the thyroid. Thus, although the radioiodine uptake was found to be decreased, the stable iodine studies showed that this was not associated with a reduction in the A.I.U. (Table I). The mean P.I.I. in the three cases studied rose from 0.11 to 1.01 $\mu\text{g./100 ml.}$, and this rise was not wholly compensated by the reduction in the thyroid iodine clearance

rate from 297 to 78 ml./min. Consequently the A.I.U. rose from a mean value of 19.8 to 32.2 $\mu\text{g.}/\text{hour}$. The increase in P.I.I. can clearly be ascribed to liberation of free iodine from D-thyroxine. This was confirmed by the finding that there was an associated rise in the urinary iodine, which was almost entirely in the inorganic form.

TABLE 1.—Results of Stable Iodine Metabolism Studies

	D-Thyroxine 4 mg. day (Mean of 3 Cases)		Pot. Iodide 3.32 mg. day (Mean of 5 Cases)	
	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment
Thyroid iodine clearance (ml. min.)	297.0	78.0	107.6	39.2
Plasma inorganic iodine ($\mu\text{g.}/100\text{ ml.}$)	0.11	1.01	0.18	4.58
Absolute iodine uptake ($\mu\text{g. hr.}$)	19.8	32.2	11.6	51.0

Stable iodine metabolism in patients given equivalent amounts of iodine (group 2) followed a similar pattern (Table 1). In this group the mean thyroid clearance fell from 107.6 to 39.2 ml./min., the P.I.I. rose from 0.18 to 4.58 $\mu\text{g.}/100\text{ ml.}$, and the A.I.U. rose from 11.6 to 51 $\mu\text{g.}/\text{hour}$. The rise in the P.I.I. in patients treated with potassium iodide (+4.40 $\mu\text{g.}/100\text{ ml.}$) was much larger than that in patients treated with D-thyroxine (+0.90 $\mu\text{g.}/100\text{ ml.}$). This may be due to defective absorption or to biliary excretion of D-thyroxine, and probably explains the more rapid fall in thyroid uptake of radioiodine in those treated with iodide.

It is evident from the Chart that there was no clinical improvement over the 12-week period in the eight patients (group 1) receiving D-thyroxine. The therapeutic index showed no significant change, and there was a small decrease in the mean body weight. No individual patient showed worth-while clinical improvement.

Group 3 (Methylthiouracil + D-Thyroxine) and Group 4 (Methylthiouracil Only)

The changes in exophthalmos in millimetres are recorded in Table II, which shows the sum of the changes in both eyes for each case. The increase represents the difference between the control measurement and the measurement obtained when the patient became euthyroid. Both groups showed a significant increase in the degree of exophthalmos: the group treated with methylthiouracil plus D-thyroxine ($2.1 \pm 1.5\text{ mm.}$) had no advantage over the control group ($1.9 \pm 1.7\text{ mm.}$). One patient (not included in Table II) developed an acute protrusion of one eye while receiving treatment with D-thyroxine and methylthiouracil. The left eye protruded 11 mm. and the right 3 mm.

TABLE II.—Effect of Treatment on the Exophthalmos in Thyrotoxic Patients

Case No.	Methylthiouracil	Methylthiouracil and D-Thyroxine
1	3 mm.	5 mm.
2	1 "	2 "
3	1 "	1 "
4	1 "	3 "
5	4 "	2 "
6	2 "	0 "
7	-2 "	2 "
8	0 "	
9	3 "	
10	2 "	
11	4 "	
12	4 "	
Mean	1.9 ± 1.7	2.1 ± 1.5

The values represent the difference in exophthalmometry readings (sum of both eyes) before and after treatment. The mean and standard deviation for each group is shown.

Discussion

No improvement was noted in the clinical features of our thyrotoxic patients after treatment with D-thyroxine. However, an effect consistently found was the reduction of the radioiodine uptake by the thyroid, but stable iodine studies indicated that the absolute iodine uptake by the thyroid in $\mu\text{g.}/\text{hour}$ increased rather than decreased. This effect was similar to that found after the administration of potassium iodide in equivalent doses. The absence of significant amounts of organic iodine compounds in the urine and the rise in the level of the plasma inorganic iodine provides further evidence that the effect of D-thyroxine was due to the liberation of iodide. In thyrotoxic patients L-thyroxine does not suppress the uptake of radioactive iodine when given in doses of 0.2 to 0.3 mg. daily. D-Thyroxine, even in doses ten times as large, appears to be equally incapable of suppressing thyroid over-activity. There is thus no evidence that D-thyroxine specifically inhibited the pituitary-thyroid axis, and its effect can be entirely explained on the basis of an increase in the extrathyroidal iodine pool arising from the iodide liberated by the breakdown of the D-thyroxine in the tissues.

The exophthalmometry readings we report confirm that administration of antithyroid drugs is followed by a worsening of exophthalmos (Dobyns and Haines, 1946), possibly owing to an increase in the pituitary exophthalmogenic factor or factors. It is clear from Table II that D-thyroxine cannot prevent this increase in exophthalmos.

We conclude that D-thyroxine in the doses used is of no value in the treatment of thyrotoxicosis or of the associated exophthalmos.

Summary

No improvement in the clinical features of eight thyrotoxic patients was found after the administration of D-thyroxine. The increase in exophthalmos produced by antithyroid drug therapy was not prevented by concurrent D-thyroxine administration.

Studies of stable iodine metabolism showed no suppression of the iodide-trapping mechanism of the thyroid. The fall in thyroid uptake of radioiodine during treatment with D-thyroxine was shown to be due to liberation of iodide.

It is concluded that D-thyroxine in the dose range used is of no value in the treatment of thyrotoxicosis or of the associated exophthalmos.

We thank Professor E. J. Wayne for permission to treat these cases and for his helpful advice and encouragement. We are indebted to Dr. R. D. Hunter for carrying out the exophthalmometry readings. Glaxo Laboratories Ltd. generously supplied all the D-thyroxine and potassium iodide tablets used. This study was supported in part by grants from the Secretary of State for Scotland on the recommendation of the Advisory Committee of Medical Research, and from the Medical Research Council.

REFERENCES

- Boyd, G. S., and Oliver, M. F. (1960). *J. Endocr.*, **21**, 33.
 Crooks, J., Murray, I. P. C., and Wayne, E. J. (1959). *Quart. J. Med.*, **28**, 211.
 —, Wayne, E. J., and Robb, R. A. (1960). *Lancet*, **1**, 397.
 Dobyns, B. M., and Haines, S. F. (1946). *J. clin. Endocr.*, **6**, 633.
 Farrell, L. P., and Richmond, M. H. (1961). To be published.
 Greene, R., and Farran, H. E. A. (1958). *Brit. med. J.*, **2**, 1057.
 Koutras, D. A., Alexander, W. D., Buchanan, W. W., Crooks, J., and Wayne, E. J. (1960). *Lancet*, **2**, 784.
 Starr, P., and Liebhold-Schueck, R. (1953). *Arch. intern. Med.*, **92**, 880.