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CLINICAL RESEARCH

Thyroid Insufficiency. Is Thyroxine the Only Valuable Drug?

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Abstract

Purpose: *To evaluate the efficacy of a drug containing both liothyronine and thyroxine (T3 + T4) in hypothyroid patients who were treated, but not cured, with thyroxine (T4 alone).*

Design: *Practice-based retrospective study of patients' records.*

Materials and Methods: *The records of 89 hypothyroid patients, treated elsewhere with thyroxine but still with hypothyroidism, seen in a private practice in Antwerp, Belgium, were compared with those of 832 untreated hypothyroid patients, over the same period of time (May 1984–July 1997).*

Results: *The same criteria were applied to both groups: a score of eight main symptoms of hypothyroidism and the 24 h urine free T3 dosage. The group of 89 patients, treated elsewhere with T4, but still complaining of symptoms of hypothyroidism, did not really differ from the group of untreated hypothyroid patients as far as symptoms and 24 h urine free T3 were concerned. A number of these patients were followed up during treatment with natural desiccated thyroid (NDT): 40 T4 treated patients and 278 untreated patients. Both groups responded equally favourably to NDT.*

Conclusions: *Combined T3 + T4 treatment seems to be more effective than treatment with T4 alone in hypothyroid patients.*

Keywords: hypothyroidism, natural desiccated thyroid, Armour Thyroid, combined T3 + T4, thyroxine, liothyronine, triiodothyronine, 24 h urine free T3.

INTRODUCTION

Having prescribed routinely for many years a natural thyroid hormone (Thyranon), containing both liothyronine (T3) and thyroxine (T4), as well as a combined synthetic T3 + T4 drug (Novothyral, containing 20 μg T3 and 100 μg T4), we had the opportunity in 1974 to prescribe a new T4-only drug (Euthyrox, commercially available in Belgium since August 1978). After less than six months, we ascertained the inability of this new T4 alone drug to produce clinically the same results as the previously used combined drugs. From 1984 on, when finally a reliable test—the 24 h urine free T3 test—became available, we were able to quantify this.

MATERIALS AND METHODS

As published earlier in this journal [1], we have shown that the majority of symptoms and

† Died 21 July 1997.

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TABLE 1. Age and sex distribution in 89 thyroxine treated and 832 untreated hypothyroid patients, compared respectively with 40 and 278 of them subsequently treated with NDT

	Number	Mean age	SD
Thyroxine treated patients			
Total group	89	46.60	10.46
Women	85	46.70	13.52
Men	4	44.50	6.87
Untreated patients			
Total group	832	43.11	13.94
Women	676	43.06	14
Men	156	43.35	13.4
Early thyroxine, now NDT treated			
Total group	40	43.30	11.02
Women	36	43.16	11.19
Men	4	44.50	6.87
Early untreated, now NDT treated			
Total group	278	43.08	12.09
Women	228	43.20	12.07
Men	50	42.70	11.77

signs of hypothyroidism can be reduced to a list of eight main symptoms. We quantified each symptom as follows:

"0" indicates the absence of the symptom, representing the normal status;
"2" indicates the full-blown presence of the symptom; while
"1" indicates an intermediate state.

Thus one single patient can present with a maximum score of 16 if the 8 main symptoms are all clearly present. And if all 89 and all 832 patients present with 8 symptoms, i.e. with a total symptom score of 16, the prevalence of that symptom is represented by 100%. Thus, the symptoms can be compared before and after treatment.

The laboratory test which we found to be the most reliable was the 24 h urine free T3 test. As treatment in this study we prescribed the combined T3 + T4 drug, natural desiccated thyroid (NDT).

Subjects

We reviewed the records of 89 Caucasian hypothyroid patients, treated elsewhere with T4 alone, but still with hypothyroid symptoms. As far as age and sex distribution were concerned (Table 1) they were roughly comparable with those of the main group consisting of 832 untreated hypothyroid patients. From the 89 T4 treated group 40 patients (4 men and 36 women) could be followed up after treatment with NDT. From the 832 untreated group 278 patients (50 men and 228 women) could be followed up after treatment with NDT.

Laboratory Techniques

Determinations of 24 h urine free T3 were performed in the Antwerp Central Laboratory, following a technique described in an earlier issue of this journal [1].

Drugs Used

The brand names of the Levothyroxine preparations used by the 89 patients were Elthyrone (60 patients), Elthyroxine (4 patients), Euthyrox (15 patients), and Thyrax (10 patients), in

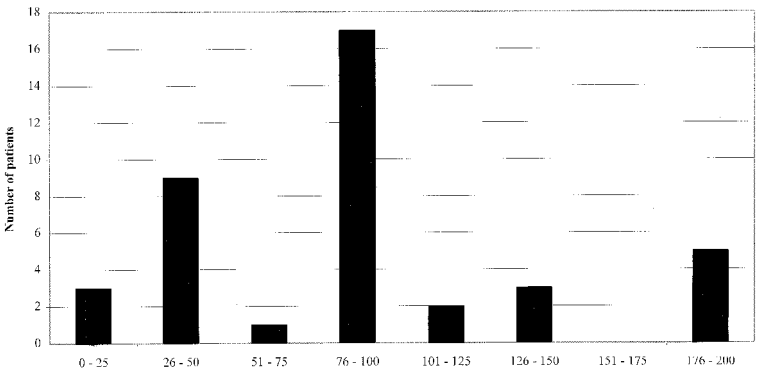

FIG. 1. Distribution of thyroxine dosage.

dosages varying between 25 and 225 μg/day, 98.4 μg on average (see Fig. 1). Thyroxine is available in tablets of 25, 50, 100, 115 and 200 μg. Only 5 patients took less than 50 μg thyroxine/day, but 84 patients took more over a long period. The duration of the last level of treatment varied between 2 weeks and 10 years, 38.55 months on average, i.e. more than 3 years. Only 2 patients took thyroxine treatment for less than 2 months. This allows us to eliminate the eventual objection of summation over time owing to another drug prescribed later on, as well as the objection of spontaneous remission. The situation in the group of 40 patients followed up under NDT treatment was comparable with that of the 89 patients: on average they took 99.7 μg thyroxine over a period of 33.2 months.

Natural desiccated thyroid, commercially available as Armour Thyroid (Thyroid Tablets, USP), manufactured for Forest Pharmaceuticals, Inc., St Louis, MO 63043, USA, by Rhône-Poulenc-Rorer Pharmaceuticals, Inc., Fort Washington, PA 19034, USA, was procured by individual patients at local chemist shops. Armour Thyroid tablets contain 23 μg T3 for each 100 μg T4 and are available in 15, 30, 60, 90, 120, 180, 240 and 300 mg tablets. The dosage of NDT was increased by 30 mg/day every 2 weeks. The treatment was adjusted for the first time after $2\frac{1}{2}$ months, later after 3 months, according to clinical status. Patients under NDT treatment were at first biologically (24 h urine T3) controlled after 6 or 12 months, and later every 1 or 2 years. The NDT end-dosage varied between 150 and 300 mg/day, 233 mg/day on average, after $4\frac{1}{2}$ to 72 months, 26.9 months on average. This eliminates the eventual placebo effect of a new drug.

Statistical Methods

All statistical calculations were executed on Excel for Windows 95.

RESULTS

Thyroxine Treated Patients

In the 89 T4 treated hypothyroid patients the prevalence of symptoms was comparable with that of the main group of 832 untreated hypothyroid patients (see Fig. 2). This was also the case with the 278 untreated and the 40 T4 treated patients who could be followed up under NDT treatment.

Under T4 treatment the mean number of symptoms reached 10.72 ($\pm$3.17), while the mean 24 h urine free T3 was 797.5 pmol ($\pm$299), parameters similar to those of the untreated patients, the optimal reference values being respectively no symptoms at all and 2000 pmol free T3 24 h urine.

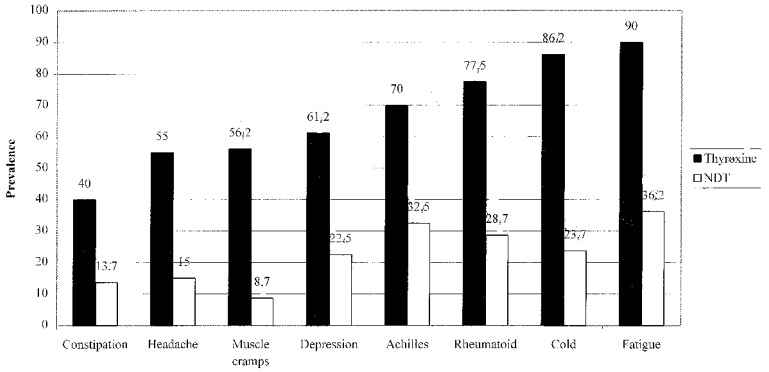

FIG. 2. Score of symptoms under T4 and under NDT.

Table 2 shows the data of both total and followed up groups of patients without treatment, under thyroxine and under NDT treatment.

NDT Treated Patients

The prevalence of symptoms before and after treatment. Figure 2 shows the prevalence of the 8 selected main symptoms as a percentage before and during treatment with NDT—100% being the number of patients (respectively 89 and 40) multiplied by 16, the maximum score. Under treatment with NDT, the prevalence score of the 8 selected symptoms dropped dramatically from 90% for fatigue and 40% for constipation, to residual values of 36.2% and 13.7%, respectively. Under treatment with NDT the mean score of symptoms dropped from 10.72 ($\pm$ 3.17) to 3.6 ($\pm$ 2.6). The mean 24 h urine T3 rose from 767 pmol ($\pm$ 299) under T4 treatment to 1990 pmol ($\pm$ 522) under NDT treatment. These figures were similar to those of the untreated hypothyroid patients before and during treatment with NDT (Table 2 and Figures 3 and 4).

DISCUSSION

This study does not preclude the possibility that T4 can cure certain patients with hypothyroidism. Indeed, patients who are able to convert the inactive prohormone T4 into

TABLE 2. Symptoms score and 24 h urine free T3 in 89 T4 treated patients, of which 40 were subsequently treated with NDT, compared with 832 untreated hypothyroid patients of which 278 were subsequently treated with NDT

	Untreated 832	Untreated 278	T4 treated 89	T4 treated 40
Symptoms score	10	10.1	10.4	10.7
Urine T3 pmol	756	752	767	797.5
Months treatment	—	—	38.6	33.2
Thyroxine μg	—	—	97.6	99.7
		NDT treated 278		NDT treated 40
Symptoms score		3.6		3.6
Urine T3 pmol		1900		1990
Months treatment		23		26.9
NDT mg		200		233

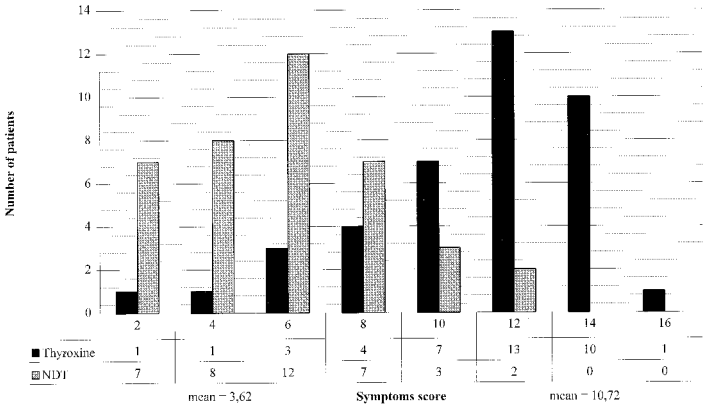

FIG. 3. Symptoms score under T4 and under NDT.

the active hormone T3 by liver- and kidney-produced 5′-deiodase can be cured by T4 alone. Thyroxine itself has little or no biological activity, and tissue effects attributed to T4 can indeed only be explained by conversion of T4 into T3 [2]. The cell receptors exclusively bind T3.

We did not conduct a double-blind trial, comparing the effects of T4 with those of placebo. We had bad clinical experiences with T4 (Euthyrox) some years ago, and considered it unethical in this case to submit our patients to such a treatment. We had, however, the opportunity to meet hypothyroid patients who had been treated elsewhere with T4 and were still complaining of hypothyroid symptoms. These patients improved with the combined T3 + T4 treatment (NDT).

We also had the opportunity to meet patients, suitably stabilized under NDT, who had been taken off NDT by their GP and reinstated on T4, who presented with the same symptoms as before. Renewed treatment with NDT corrected the situation.

Improvement under NDT treatment cannot be attributed simply to a placebo effect. A placebo effect rarely exceeds a 25% improvement. In this study the improvement range averaged 69.15% and varied between 53.6% and 84.5% according to the symptom examined, as shown in Fig. 2.

Further proof of the efficacy of combined T4 + T3 treatment is continuing improvement over the months and years, with an increase in improvement over time if treatment is taken faithfully at the same dosage.

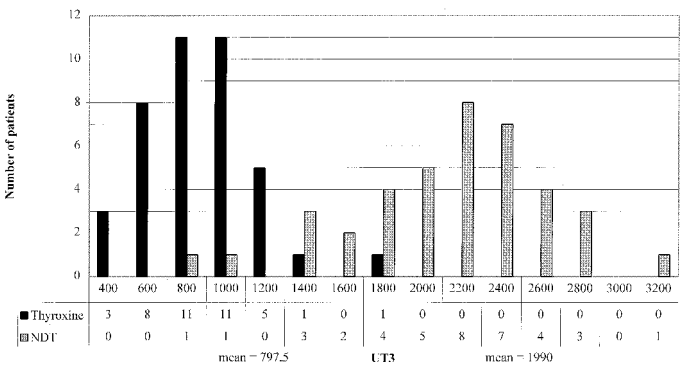

FIG. 4. 24 h urine T3 in pmol under T4 and under NDT.

It is probable that practitioners who rely more on serum tests (thyroid stimulating hormone [TSH] and free T4) than on clinical signs and 24 h urine free T3 do not prescribe a sufficient dose of thyroid hormone to obtain satisfactory results. Carr *et al.* [3] observed, in a study performed on 21 patients, that those patients who were allowed to define the T4 dose themselves preferred a dose that was on average 50 μg/day higher than the one that their practitioner would have prescribed for them to obtain a serum TSH concentration within the reference interval.

Endocrinologist Dr Bayliss, referring to a survey of the correspondence from 174 hypothyroid patients who wrote to the British Thyroid Foundation, draws attention to the fact that restoration to the euthyroid state in most patients will be achieved with a dose of T4 which results in a normal or slightly raised serum T4 concentration and that patients feel at their best when the serum total and free T4 concentrations are towards the upper end of the reference range or slightly above it. Most patients were being undertreated [4]. We do, however, not consider raising the T4 dose to be the right method.

It is necessary to stress that the clinical evaluation of a patient's condition must precede interpretation of laboratory tests and not follow it; furthermore, hypothyroidism means low peripheral metabolism, be that because of a hypothalamic, hypophyseal or thyroidal disturbance, renal or hepatic insufficiency to synthesize 5′-deiodase or peripheral nuclear T3 receptor incompetence. The patient's thyroid insufficiency has in each case to be treated with the most appropriate drug, to restore the patient to the euthyroid state, i.e. with the lowest possible number of symptoms.

In a study by McGavack in 1956 involving 12 myxoedematous patients during 60 trials [5] it was established that a mean optimal dose of 258 μg (200–350) sodium-l-thyroxine was required to bring patients to a euthyroid state, whereas 152.6 mg (120–210) NDT (which contains approximately 22.5 μg T3 and 95 μg T4), and 145 μg (100–175) d-l-triiodothyronine sufficed to keep them in a balanced euthyroid state. This is proof that the best results are obtained with combined T4 + T3 treatment. According to McGavack, the time required to bring the subjects from the euthyroid state back to myxoedema after withdrawal of the drug was 31.7 days for NDT, 26.4 days for T4 and 9.8 days for triiodothyronine. This prompted us, when starting treatment with NDT, to increase the dose gradually, and very slowly, to permit adaptation of the metabolism.

In a first double-blind cross-over study on this subject by Nyström *et al.* [6] in 1988, which set out to evaluate whether thyroxine was of any benefit in the treatment of hypothyroidism, a group of 17 subclinically hypothyroid women, without any clinical evidence of thyroid disease, with total T4, free T4 and free T3 concentrations within the reference interval, but with an excessive TSH response to TRF, were followed up during two consecutive periods of 6 months. These patients were treated with a mean of 150 μg l-thyroxine or placebo. Treatment was considered beneficial if patients scored better in at least two psychometric tests and correctly identified the period of effective treatment with a subjective impression of improvement in their physical condition. Only four out of the 17 female patients improved during thyroxine treatment, so the authors concluded that only one in four (25%) subclinical hypothyroid women will benefit from T4 treatment.

In a study performed on 33 subclinical hypothyroid patients (diagnosis based on moderately elevated TSH only), only 8 out of 17 patients (47%) improved symptomatically after six months' unchanged optimal T4 treatment (the mean dosage was 71.2 μg/day ± 7 μg), whereas no less than 3 out of 16 patients (18.7%) improved symptomatically during placebo administration [7].

Skinner *et al.* [8] studied the clinical response to thyroxine sodium replacement in 139 clinically hypothyroid but biochemically euthyroid patients (TSH and/or free T4 being within 95% of laboratory reference intervals) who presented with six or more out of 16 pivotal clinical criteria. Diagnosis was established and treatment adjusted according to clinical findings only. Eighty point one percent of clinical hypothyroid features disappeared or improved in 93% of the patients during thyroxine treatment, while only 19.9% remained

unchanged or worsened. The global symptoms score fell from 13.3 to 3 after a minimum period of 6 months' optimal treatment. There was a significant correlation between clinical response and thyroxine replacement dosage. The mean optimal dosage was not mentioned by the author. No gradation in symptoms was mentioned either.

In order to assess whether the addition of T3 to T4 was of any benefit, Bunevicius [9] observed 33 hypothyroid patients after near total thyroidectomy or thyroiditis dependent on exogenous thyroxine, treated with a mean of 175 μg levothyroxine daily, during two periods of five weeks. During one of these periods 50 μg T4 was replaced by 12.5 μg triiodothyronine in a cross-over manner. Cognitive test scores, mood assessment and symptom scores were closer to normal and most patients felt better during the administration of the combined therapy. The initial dosage of baseline thyroxine had no influence on the benefit of the adjunction of triiodothyronine. TSH remained comparable during both treatments, proving the inadequacy of TSH measurement. Five weeks of treatment seem to be a rather short period in our opinion.

Similarly, in a study by Cooke *et al.* [10] the addition of 15 to 50 μg triiodothyronine/day resulted in a marked decrease in depression in 7 out of 9 patients (77.7%) under T4 therapy who responded inadequately to antidepressant therapy.

For a period of 3 weeks Joffe and Singer added 37.5 μg T3 to 150 μg T4 in 38 clinically and biochemically euthyroid subjects with major depression, who had failed in an adequate trial with desipramine. They observed T3 to be more effective than T4 in curing depression in 54% of patients. They suggest that depression is a state of relative T4 excess [11]. Here too 3 weeks is a very short period.

The present comparative study, which comprises clinically hypothyroid patients, allows us to state that hypothyroid patients who continue to complain of hypothyroid symptoms, while on treatment with thyroxine (T4 alone), can favourably be treated with a drug combining T3 and T4. The dose adjustment depends on the clinical symptoms. One has to wait 8 weeks with each dose increase to find a new steady state. Four months' treatment seems the minimum period to obtain substantial results.

CONCLUSION

Combined T4 + T3 treatment is definitely more efficient than T4 treatment alone. Since the TSH is chiefly regulated by feedback from the inactive prohormone T4, rather than with the active hormone T3, the reliable 24 h urine free T3 test should preferably be used instead.

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