Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment

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SUMMARY. Examination of thyroxine usage in a study in the United States of America revealed that many patients were prescribed thyroxine for non-thyroid indications, such as obesity and fatigue. Many of those receiving thyroxine had high or low serum thyroid stimulating hormone levels, indicating prescription of incorrect doses or lack of patient compliance with therapy. Long term thyroxine therapy may have effects upon the risk of osteoporosis. The aims of this study were to investigate indications for thyroxine prescription in the United Kingdom and to examine the frequency of abnormal serum thyroid stimulating hormone concentrations in those prescribed thyroxine for hypothyroidism. This was in order to determine the relevance of measurement of thyroid stimulating hormone level in monitoring thyroxine therapy. Subjects receiving thyroxine were identified from the computerized prescribing records of four general practices in the West Midlands. Of 18 944 patients registered, 146 (0.8%) were being prescribed thyroxine; 134 of these had primary hypothyroidism and the remainder had other thyroid or pituitary diseases prior to treatment. Of the 97 patients with primary hypothyroidism who agreed to have their thyroid stimulating hormone level measured, abnormal serum levels were found in 48%, high levels in 27% and low levels in 21%. There was a significant relationship between prescribed thyroxine dose and median serum thyroid stimulating hormone level: high hormone levels were found in 47% of those prescribed less than 100 μg thyroxine per day, while low levels were found in 24% of those prescribed 100 μg or more. Thus, thyroxine prescription was common in the four practices sampled, although indications for its use were appropriate. The frequency of abnormal thyroid stimulating hormone level results in those prescribed thyroxine for hypothyroidism, and the relationship between dose and hormone level suggest that undertreatment and overtreatment are common and largely reflect inappropriate dose prescription.

Keywords: thyroid hormones; inappropriate prescribing; drug dosage; thyroid function tests; hypothyroidism.

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Introduction

HYPOTHYROIDISM is a common disorder, a large screening study in the north of England revealing a prevalence of up to 19 cases per 1000 women.[1] A prevalence study of a local population showed that 3.6% of those aged 60 years and over received thyroxine therapy,[2] while in the United States of America, up to 7% of a sample population over 58 years were prescribed thyroxine.[3]

Hypothyroidism represents a clear indication for thyroxine therapy but examination of thyroxine usage in the USA revealed that of 178 elderly people receiving thyroxine, 32% of men and 13% of women were being prescribed thyroxine for non-thyroid indications including obesity, fatigue and hypercholesterolaemia.[3] Since thyroxine therapy may not be without long term consequences, especially in terms of effects upon bone density and risk of osteoporosis,[4,5] it is important to establish whether in the United Kingdom there is a similarly high prevalence of thyroxine prescription for inappropriate indications. Furthermore, the screening study in the USA indicated that of those prescribed thyroxine, 22% had serum thyroid stimulating hormone concentrations outside the normal range, a finding which suggests that prescribed doses were inadequate or excessive, or that non-compliance with treatment was common. A study of patients attending a thyroid clinic in the UK has similarly revealed a prevalence of abnormal thyroid stimulating hormone levels of 39.5% in those taking thyroxine for hypothyroidism.[6]

The first aim of this study was to investigate indications for thyroxine treatment in the UK by examining prescriptions of thyroxine in four general practices. The second objective was to determine the relationship between prescribed dose of thyroxine and serum thyroid stimulating hormone values (measured using an assay capable of measuring values above or below the reference range) in those receiving thyroxine for hypothyroidism, in order to investigate the relevance of biochemical testing in the monitoring of thyroxine doses and compliance with treatment.

Method

Patients receiving thyroxine therapy were identified by J P using the computerized prescribing records of four general practices in the West Midlands. Practices were identified by personal contact and were asked to recruit patients receiving thyroxine. No practice refused to take part and none, at the time of the study, had a special interest in thyroid disease.

The records of all patients on thyroxine therapy were examined to determine the indication for treatment. In addition, the records of those patients with primary hypothyroidism who were willing to have their serum thyroid stimulating hormone level measured were examined to ascertain the age of the patient, duration of treatment and prescribed thyroxine dose.

Venous blood samples were kept at 4 °C until centrifugation and serum was then frozen at −70 °C until assayed. All samples were measured at the same laboratory. Serum thyroid stimulating hormone level was measured using a commercial immuno-

radiometric assay (Gamma-BCT® , IDS). During the period of the study, the detection limit of the assay was 0.05 mU l^{-1}; the reference range for thyroid stimulating hormone level was 0.4 to 4.5 mU l^{-1}, as described previously.[2] Serum free thyroxine values were measured in those with thyroid stimulating hormone level results outside the reference range using an Amerlex M® (Amersham International) radioimmunoassay kit (normal range 9.0 to 24.0 pmol l^{-1}) as described previously.[2]

Analysis

Kruskal-Wallis analysis of variance was used to analyse the variation in thyroid stimulating hormone concentrations with different thyroxine doses; a non-parametric analysis was used because the distribution of thyroid stimulating hormone values was non-Gaussian.

Results

Indications for thyroxine treatment

Of the 18 944 patients registered with the participating practices in 1990, 146 (0.8%) were prescribed thyroxine; all of the patients were receiving thyroxine for endocrine indications. A total of 134 patients (91.8%) had biochemical evidence of primary thyroid failure prior to commencement of thyroxine therapy. Thyroid function tests indicated overt hypothyroidism in 120 of these patients. One hundred and thirteen patients had low total serum thyroxine level or low free thyroxine with elevated serum thyroid stimulating hormone level. Six patients had low serum protein bound iodine levels and one patient had low basal metabolic rate. Subclinical hypothyroidism was found in 14 patients (raised serum thyroid stimulating hormone levels with normal thyroxine values). Of the other 12 patients, nine (6.2%) were on thyroxine treatment for thyroid indications other than hypothyroidism: two had a past history of thyroid cancer and seven had thyroid nodules or goitre. Three patients (2.1%) were receiving thyroxine for hypothyroidism secondary to hypopituitarism.

Serum thyroid stimulating hormone concentrations in patients receiving thyroxine for hypothyroidism

Of 5534 patients at Practice A, 36 were receiving thyroxine therapy for hypothyroidism and 33 of them (91.7%) agreed to have a thyroxine stimulating hormone assay. Of 2918 patients at Practice B, 31 were receiving thyroxine and 21 (67.7%) agreed to the assay. At Practice C, 35 out of 6510 patients were on thyroxine and 22 (62.9%) agreed to an assay; at Practice D, of 3922 patients 32 were on thyroxine and 21 (65.6%) agreed to the assay. Therefore, of the 134 patients receiving thyroxine therapy for hypothyroidsim 97 (72.4%) had a thyroid stimulating hormone assay.

Of these 97 patients, 83 (85.6%) were women, with a mean age of 58 years (range 32 to 87 years); they had been prescribed thyroxine for a mean of eight years (range six weeks to 26 years). The 14 men on thyroxine (14.4%) had a mean age of 62 years (range 42 to 78 years); they had been prescribed thyroxine for a mean of seven years (range six weeks to 11 years). Eighty seven per cent had had thyroid function tests within the preceding three years. There was no difference in the frequency of previous testing between the four participating practices.

Fifty one patients had serum thyroid stimulating hormone level values within the normal range (0.4–4.5 mU l^{-1}). Serum thyroid stimulating hormone values above the reference range were found in 26 of the 97 patients (26.8%) prescribed thyroxine for primary hypothyroidism and were greater than 10.0 mU l^{-1} in 13 of these 26 patients. One of the 26 patients with an elevated serum thyroid stimulating hormone level had a free thyroxine value below the reference range. Thyroid stimulating hormone values below the lower limit of the reference range were found in 20 of the 97 subjects tested, with seven of these having thyroid stimulating hormone concentrations below the detection limit of the assay employed. Seven patients (five with undetectable thyroid stimulating hormone levels) had free thyroxine concentrations above the reference range.

Of 19 patients prescribed thyroxine in a dose of less than 100 μg per day, nine (47.4%) had thyroid stimulating hormone values above the upper limit of normal (four had values greater than 10.0 mU l^{-1}) and one had a thyroid stimulating hormone value below the lower limit of the normal range. Of those 70 prescribed 100 μg or more but less than 200 μg of thyroxine per day, 15 (21.4%) had high thyroid stimulating hormone concentrations and 17 (24.3%) had low values, with five subjects (7.1%) having thyroid stimulating hormone results below the limit of assay detection. Eight patients were prescribed 200 μg or more of thyroxine per day, and of these, two had undetectable thyroid stimulating hormone levels and two had thyroid stimulating hormone levels greater than 10.0 mU l^{-1} (18.2 mU l^{-1} and 20.9 mU l^{-1}, respectively).

The median serum thyroid stimulating hormone values in the treated hypothyroid patients, divided into four groups according to prescribed thyroxine dose, are shown in Table 1. In those prescribed less than 200 μg of thyroxine per day, the median serum thyroid stimulating hormone value fell as the prescribed dose of thyroxine increased. In addition, there was a significant difference between the median thyroid stimulating hormone values for all doses of thyroxine ($P<0.01$). The mean thyroxine dose in those patients with normal serum thyroid stimulating hormone concentrations was 114 μg per day.

Table 1. Median concentrations of serum thyroid stimulating hormone in patients treated with thyroxine for hypothyroidism, according to prescribed dose of thyroxine.

Thyroxine (μg day^{-1})	No. of patients	Median serum TSH (mU l^{-1})
<100	19	4.5
100	51	2.4
>100 to <200	19	1.2
⩾200	8	1.8

TSH = thyroid stimulating hormone.

Discussion

This study of patients from four general practices in the UK has revealed a prevalence of thyroxine treatment of 0.8%. This figure is in accord with the results of the Whickham survey carried out in the north of England[1] and other surveys of the prevalence of treated hypothyroidism.[3] While such surveys indicate that thyroxine treatment for known cases of hypothyroidism is common, it is likely that further cases of thyroid failure go unrecognized in the absence of screening programmes for hypothyroidism.[2]

In contrast to the situation in the USA where an investigation of patients taking part in the Framingham study revealed that 13% of women and 32% of men treated with thyroxine were taking it for reasons such as obesity or fatigue (indications currently not thought appropriate[3]), all patients in the present survey were found to be taking thyroxine for clear thyroid or pituitary abnormalities. The most frequent indication for thyroxine therapy was overt thyroid failure (120 patients), while a considerable number of patients (21) were treated for 'subclinical' hypothyroidism or because of thyroid enlargement, the latter

group having indications for thyroxine treatment which are accepted although less well established.[7,8]

Measurement of serum thyroid stimulating hormone level in those prescribed thyroxine for hypothyroidism revealed that the thyroid stimulating hormone value was outside the reference range in almost half of the cases (47%), with approximately one quarter (27%) having a result above normal (half of these with a level above 10.0 mU l^{-1}) and one fifth below normal (one third of these had undetectable thyroid stimulating hormone levels). These findings are similar to those of the Framingham study which revealed that of those treated for definite hypothyroidism, 20% had insufficient thyroid therapy (indicated by a raised serum thyroid stimulating hormone level) when last seen.[3] The present community based survey has revealed a higher prevalence of abnormal thyroid stimulating hormone level results than reported in a survey of patients with treated hypothyroidism regularly attending a thyroid clinic, in whom the prevalence was 39%.[6]

The clear relationship between the median serum thyroid stimulating hormone level result and the prescribed dose of thyroxine provides good evidence that abnormal thyroid stimulating hormone values largely reflect prescription of inadequate or excessive doses of thyroxine. Poor compliance with treatment was also likely to play a part, especially in those subjects prescribed thyroxine at a dose of 100 μg per day or more in whom an elevated serum thyroid stimulating hormone was found. This is shown by the follow-up results of the two patients on 200 μg of thyroxine who initially had high thyroid stimulating hormone concentrations of 18.2 mU l^{-1} and 20.9 mU l^{-1} but in whom the thyroid stimulating hormone value fell subsequently to within normal values despite remaining on the same daily dose; it seems likely that this was a result of improved compliance, although there was no definite evidence.

While elevation of serum thyroid stimulating hormone level was accompanied by a reduction in circulating free thyroxine in only one patient, the marked prevalence of inadequate therapy with thyroxine, indicated by a raised thyroid stimulating hormone level, may have important consequences in view of reported adverse effects of mild hypothyroidism upon circulating lipids and upon the risk of ischaemic heart disease.[9-11] Conversely, there is increasing concern regarding the long term consequences of doses of thyroxine associated with suppression of thyroid stimulating hormone levels or elevation of circulating thyroxine in terms of effects upon bone density and risk of osteoporosis.[4,5,12] While long term adverse effects of minor degrees of undertreatment or overtreatment with thyroxine upon ischaemic heart disease or bone fracture risks have yet to be proven, these concerns regarding thyroxine therapy, and the ability to detect minor degrees of hypothyroidism or hyperthyroidism clinically in such patients,[6,13] argue in favour of regular, perhaps annual, assessment of thyroid function in subjects prescribed thyroxine. It is therefore suggested that general practitioners and others caring for patients receiving replacement thyroxine therapy should adjust dosage and encourage compliance so that thyroid stimulating hormone values, measured in a sensitive assay, are close to or within the normal range. Further research is indicated to determine how often such biochemical monitoring should be performed.

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