Drugs That Interact With Levothyroxine

An Observational Study From the Thyroid Epidemiology, Audit and Research Study (TEARS)

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Abstract and Introduction

Abstract

Objective The aim of this study was to determine the extent of drug interactions affecting levothyroxine, using study drugs often co-administered to patients on long-term levothyroxine therapy.

Design A retrospective population analysis linking biochemistry and prescription data between 1 January 1993 and 31 December 2012 was used.

Patients The study population was Tayside residents prescribed levothyroxine on at least three occasions, within a six-month period, prior to the start of a study drug. Individuals acted as their own controls pre- and postinitiation of study drug. Overall, 10 999 patients (mean age 58 years, 82% female) being treated with thyroxine were included in the study.

Measurements Changes in TSH following initiation of study drug.

Results Iron, calcium, proton pump inhibitors and oestrogen all increased serum TSH concentration: an increase of 0·22 mU/l ($P < 0.001$), 0·27 mU/l ($P < 0·001$), 0·12 mU/l ($P < 0·01$), and 0·08 mU/l ($P < 0·007$), respectively. For these four study drugs, there was a clinically significant increase of over 5 mU/l in serum TSH, in 7·5%, 4·4%, 5·6% and 4·3% patients, respectively. There was a decrease of 0·17 mU/l (*P*-value 0.01) in the TSH concentration for those patients on statins. The TSH decreased by 5 mU/l in 3·7% of patients. There was no effect with H_2 receptor antagonists or glucocorticoids.

Conclusion This large population-based study demonstrates significant interaction between levothyroxine and iron, calcium, proton pump inhibitors, statins and oestrogens. These drugs may reduce the effectiveness of levothyroxine, and patients' TSH concentrations should be carefully monitored.

Introduction

The number of patients treated with thyroxine has increased from 3·12% of the female population and 0·51% of the male population in Scotland in 1994 to 5·14% and 0·88%, respectively, by 2001.[1] In Western society, the most common cause of hypothyroidism is autoimmune thyroiditis.[2] As symptoms and signs of hypothyroidism are neither sensitive nor specific, laboratory assessment of thyroid status is used to confirm the hypothyroid state. TSH is exquisitely sensitive to the plasma concentration of free thyroid hormones and is used to assess the adequacy of levothyroxine (thyroxine) replacement therapy.[3]

Absorption of thyroxine must be efficient and consistent in order for a patient to experience the sustained benefits of treatment. A direct measure of thyroxine absorption is difficult to obtain and so it is important to monitor TSH concentrations to determine pharmacological thyroid homeostasis.[4,5] Many factors[6,7] such as patient compliance, physiological disturbances, drug–drug interactions and mal-absorptive disease states can increase a patient's dosage requirements for thyroxine. Absorption of thyroxine is pH dependent, and on average 60–80% of the dose administered reaches the systemic circulation within three hours.[2,6–8] Thyroxine has its best therapeutic value if taken 1 h prior to breakfast to ensure optimum stomach acidity for absorption.[8]

Specific drugs, such as amiodarone, lithium and iodine, are known to affect thyroid status. Other drugs are thought to interact with thyroxine replacement causing it to be absorbed less effectively. Studies[9–11] have shown that the simultaneous administration of thyroxine and ferrous sulphate causes a recurrence of the hypothyroid state in some patients. This is due to iron binding to thyroxine, disrupting absorption and decreasing the amount of thyroxine available in the circulation. Oestrogen affects levels of free circulating thyroid hormone by increasing the amount of thyroid binding globulin, which binds to free hormone in the circulation.[12] Patients who are taking oestrogen hormone replacement often have to increase their dose of thyroxine to compensate. Calcium carbonate is commonly used as an antacid or to reduce the risk of osteoporosis in menopausal women. Free hormone levels are reduced in patients with long-term thyroxine replacement during co-administration of calcium.[13] Thyroxine adsorbs to calcium carbonate in an acidic environment, decreasing the bioavailability of thyroxine, causing an increase in serum TSH due to lack of thyroid hormone in the circulation. Studies[9–13] indicating these interactions were either case studies ($n = 1$) or small uncontrolled clinical trials where the number of patients were below 20. It is therefore difficult to know whether the results can be transferred to the general population of patients and what proportion of patients are affected.

Due to the effect of antacids and the requirement for a specific stomach pH for optimal thyroxine absorption, acid suppressants may also have an effect on thyroxine. Proton pump inhibitors (PPIs) suppress acid production in the stomach and are commonly prescribed for patients with gastric reflux, stomach ulcers and for use in *H. pylori* eradication. Current studies[14–18] examining PPI interactions with thyroxine are inconclusive and have used a small number of patients, healthy volunteers or *in vitro* studies to reach their conclusion. The objective of this study is to determine which drugs, both those in common use and those determined high risk, affect thyroxine absorption and/or metabolism and to ascertain what proportion of patients may be affected.

Materials and Methods

The study was carried out using databases available at the Health Informatics Centre (HIC) of the University of Dundee. All the data sets are held by HIC under the Data Protection Act for the purposes of research and audit and anonymized after linkage using Standard Operating Procedures (SOP) (http://medicine.dundee.ac.uk/standard-operating-procedures-sops). The study was approved by the Tayside Research Ethics Committee, and permission for the case record validation audit was obtained from Tayside Caldicott Guardians. Cross-sectional data linkage was facilitated by the use of the Community Health Index (CHI) number. This is a unique 10-digit health index assigned to every person registered with a General Practice in Scotland. The CHI is used as a patient identifier for all contact within NHS health care.

Study Population

The study population consisted of Tayside residents who were 18 years and above and who were alive between 1 January 1993 and 31 December 2012. Patients were included in the study if they had at least three thyroxine prescriptions before the start of the study drug. There was a substudy looking at patients who were on an unchanged dosage of thyroxine for 18 months. Patients were excluded from the study if:

- They were on carbimazole, propylthiouracil or amiodarone within 6 months of the last thyroxine prescription.
- They had a pituitary disorder (on local database).
- They were on a study drug prior to baseline.
- Any TSH measurements were taken in the hospital setting.
- More than one study drug was initiated during the study period.

Databases

Three principal databases were used in the study population. These databases cover primary, secondary and private health care.

Tayside population demographic database: This served as a master index to provide information on gender, date of birth, date of death and dates registered with general practitioner. It was used to define the study population from which cases were identified.

Biochemistry database: This contained all thyroid function tests. TSH was measured in all patients. Free thyroxine (fT4) (10–25 pmol/l), total thyroxine (T4) (65–155 nmol/l) and total triiodothyronine (T3) (0·9–2·6 nmol/l) measurements were triggered if the TSH concentration was outside the range of 0·1–4·0 mU/l. Each entry comprised the patient's anonymized CHI, the test performed, date and the results. All biochemistry tests were carried out in a centralized laboratory for the region. Three TSH assays were used throughout the time frame of the study period; ACS:180 from 1993 till July 1998, ACS: Centaur from August 1998 till June 2003 and Roche Modular E170 from July 2003 onwards. The reference range for TSH concentration was quoted as 0·4–4·0 mU/l for the entire study period. During the study period, there was a primary care regional call–recall thyroid register, replaced later

by a national payment system for primary care recall of all patients taking thyroxine (Quality and Outcomes Framework).

Tayside prescription database: This contained all prescriptions dispensed from all community pharmacies in Tayside. Each entry comprised the patient's anonymized CHI, prescription date, drug name, formulation, dosage, frequency and duration. This data set was used to identify patients who were on thyroxine and study drugs. Iron and calcium were studied because of previous reports,[6,9–11,13] although these were small case series. PPIs and H2 antagonists were chosen because of their impact on stomach pH affecting absorption and also due to conflicting reports regarding interaction.[14–17] Oestrogens were chosen because of their impact on binding proteins.[12] Corticosteroids and DMARDS were chosen to see whether any potential impact was due to immunosuppressive activity or another mechanism of action. Statins were chosen because they are very commonly co-prescribed in this patient population and they are not known to effect thyroxine absorption.[19]

British National Formulary codes (listed in) were used to reference the prescriptions for drugs.

Table 1. BNF codes for study drugs

Drug name	BNF code
Iron	9·1·1·1
PPI	1·3·5
Glucocorticoid	6·3·2
Calcium	9·5·1
	9·5·2·2
H2 antagonist	1·3·1
DMARDs	10·1·3
Oestrogen	6·4·1·1
Statins	2·12

Data Analysis

TSH measurements were analysed for 1 year prior to the introduction of any study drug. This acted as a control period to identify any changes in TSH concentration during the baseline time, before study drugs were initiated.

TSH measurements after 6 months of starting the study drugs were compared with TSH measurements before the start of the study drugs. Wilcoxon signed rank test was used to test the changes in the TSH measurements as data were not normally distributed. All analyses were carried out using spss (v19.0) and sas 9.2. The proportion of patients with a TSH change

of more than 5 mU/l was analysed. A change in serum TSH concentration of this magnitude was recognized as being more likely to be of clinical significance than smaller changes.

Results

In Tayside, 10 999 residents over the age of 18 had received at least three consecutive thyroxine prescriptions, within a six-month period, and were alive between 1st January 1993 and 31 December 2012. The mean age of this population was 58·1 years, 8977 (81·6%) were female, and 1311 (11·9%) also suffered from diabetes as a comorbidity. Of these 10 999 patients, 6482 patients were concurrently prescribed a study drug and 3809 patients were on a constant dose of thyroxine for at least two years.

During 1 year prior to the study drug (), there was no significant change in TSH for any group with one exception. Prior to starting oestrogen, patients in this group had a mean decrease in TSH concentration of 1·47 mU/l ($P = 0.008$), despite being on a constant dose of thyroxine.

Table 2. Median change in serum TSH concentration during the 1 year prior to the study drug being started. This is subdivided by patient group depending on which study drug was subsequently initiated

	Median TSH prior to study drug			
	Median change	**Minimum change**	**Maximum change**	***P-value***
Iron	−0·005	−23·3	42·29	0.400
PPI	−0·06	−58·22	41·01	0.100
Glucocorticoid	0·00	−149·91	56·98	0.678
Calcium	0·02	−17·25	98·76	0.965
H2 antagonist	−0·065	−117·40	10·46	0.372
DMARDS	0·700	−75·29	13·03	0.611
Oestrogen	−0·125	−50·92	5·47	0.008
Statins	−0·005	−23·3	42·29	0.400

($n = 6482$) shows the results for all patients on thyroxine who were started on a study drug. Both the median values and interquartile ranges for baseline TSH and for TSH at least 6 months after commencing the study drug were calculated. The number of patients in each analysis varied from 96 patients on disease modifying antirheumatic drugs (DMARDs) to 1944 patients on statins. The baseline TSH used was the most recent serum TSH concentration before the study drug was initiated. An increase in serum TSH from baseline was statistically significant in four study drugs: iron, PPI, calcium and oestrogen (). A decrease in serum TSH was statistically significant in patients taking statins. There was no statistically significant change for patients taking glucocorticoids, H2 receptor antagonists or DMARDs.

Table 3. Change in serum TSH concentration 6 months after starting the study drug (interquartile range in parenthesis)

	Median TSH during study drug				
	n	**Baseline (mU/l)**	**After (mU/l)**	**Change in median (mU/l)**	***P*-value**
Iron	723	1·29 (2·49)	1·65 (3·30)	0·36	<0.001
PPI	1491	1·51 (2·64)	1·69 (2·83)	0·18	0.001
Glucocorticoid	471	1·41 (2·42)	1·35 (2·49)	−0·06	0.153
Calcium	744	1·39 (2·44)	1·64 (2·71)	0·25	0.005
H2 antagonist	530	1·25 (2·41)	1·34 (2·75)	0·09	0.182
DMARDS	96	2·18 (3·48)	1·98 (2·90)	−0·20	0.551
Oestrogen	483	1·22 (2·41)	1·37 (2·67)	0·15	0.013
Statins	1944	1·65 (2·65)	1·44 (2·52)	−0·21	<0.001

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A subset of patients (*n* = 3809) on a constant dose of levothyroxine for at least 2 years was also analysed (). The percentage of patients that had a clinically significant increase or decrease in their serum TSH of 5 mU/l is shown. Of these, the same four drugs showed a statistically significant increase in TSH concentration. There was an increase in TSH concentration of < 5 mU/l in 7·5% of patients taking iron, 5·6% of those taking PPIs, 4·4% of those taking calcium and 4·3% of those on oestrogens. There was a significant decrease in TSH concentration of < 5 mU/l in 3·7% of patients starting on statins. The results were

not significant for those patients taking glucocorticoids, H2 receptor antagonists or DMARDs.

Table 4. Change in serum TSH concentration in patients on constant dose of levothyroxine (% change in parenthesis)

	Median TSH during study drug					
	n	**Baseline (mU/l)**	**After (mU/l)**	***P*-value**	**Increase of 5 mU/l (n,%)**	**Decrease of 5 mU/l (n,%)**
Iron	429	1·23	1·45	<0.001	32 (7·5%)	14 (3·3%)
PPI	887	1·52	1·64	0.010	50 (5·6%)	28 (3·2%)
Glucocorticoid	292	1·36	1·37	0.603	12 (4·1%)	8 (2·7%)
Calcium	450	1·43	1·70	0.001	20 (4·4%)	15 (3·3%)
H2 antagonist	293	1·23	1·02	0.902	16 (5·5%)	14 (4·8%)
DMARDS	51	2·27	2·18	0.739	5 (9·8%)	4 (7·8%)
Oestrogen	258	1·18	1·26	0.007	11 (4·3%)	4 (1·6%)
Statins	1149	1·62	1·45	0.010	33 (2·9%)	43 (3·7%)

Discussion

This study shows the importance and magnitude of drug interactions with oral thyroxine at a population level and adds to the previous information from small select case series. In addition, it has demonstrated interactions with drugs not previously noted, for example PPIs. Iron, PPIs, calcium and oestrogens co-administered with thyroxine caused increased TSH concentration possibly due to decreased thyroxine absorption or through interfering with drug metabolism. It is known from previous studies[9–13] that some of these drugs may affect thyroxine absorption and/or metabolism. The median change in population TSH was small and nonsignificant (−0·005–0·7 mU/l) and unlikely to be important for the majority of patients. The relative stability of TSH levels over the course of a year prior to starting a study drug serves as a control for this patient population and leads to the conclusion that the change in TSH during study drug administration is due to the study drug affecting thyroxine.

For patients on a steady dose of thyroxine for 2 years, some experienced an increase in serum TSH of over 5 mU/l, which is likely to be of clinical significance as this places them into a biochemically hypothyroid state. At least 7·5% of patients taking iron, 4·4% of those on calcium and 4·3% of those on oestrogen experienced this clinically significant rise in serum TSH. Our population-based study shows that this is a clinically significant problem that could have public health issues for some patients.

Strengths of the study include the large cohort of patients (n = 6482), concurrently treated with thyroxine and a study drug in a clinical scenario, which makes the results clinically

relevant. The number of patients included in this study is much greater than previous studies. Other studies used healthy volunteers or small numbers of patients, and this many not adequately represent the population of patients on chronic thyroxine therapy. A clinical study of patients could be undertaken to show direct causality between a study drug and thyroxine absorption. This should be followed by pharmacokinetic trials and case-controlled studies. Weaknesses of the study include the retrospective nature of analysis. We were not able to address patient compliance issues and so do not know whether patients consistently took their tablets at the same time or in the same way. Patients with primary hypothyroidism are more likely to develop coeliac disease and pernicious anaemia which could affect thyroxine absorption and affect gastric acid concentrations. We were unable to correct for these confounding variables, but if they were to influence the results, it would have been expected to affect all drugs studied and not just a selection of them. These issues would have affected the patient population prior to initiation of a study drug, but there was no significant change in TSH during this control interval. There may be other drugs and over the counter medications that we have not examined that interact with thyroxine, such as coffee[6,20] and other products that are impossible to measure in a population-based study. In addition, the time of day thyroxine was ingested and the serum TSH measurements were taken was not standardized such that we did not account for diurnal variation. It is, however, unlikely that this would have introduced a consistent bias.

Iron is known to cause a reduction in thyroxine absorption, and guidelines[19] recommend taking iron at least 2 h after thyroxine administration. Calcium and antacids are also listed[19] as drugs that affect the absorption of thyroxine. Our study of current clinical practice suggests that either this advice is ignored or it is inadequate to prevent drug interaction for a significant number of patients.

Previous studies that have looked at the effect of PPIs on thyroxine absorption have been inconclusive. Pabla *et al*.[14] used an *in vitro* model to show that dissolution of thyroxine decreased with an increase in pH, suggesting a link between patients on concurrent thyroxine and PPI therapy. Further studies[15,16] concluded that both omeprazole and lansoprazole therapy increased serum TSH in patients also treated on thyroxine. Two studies[17,18] noted no difference in thyroxine absorption after PPI administration. These studies concluded that acidity of the stomach does not play a role in absorption of thyroxine, but rather other factors, such as competition and adsorption processes, may affect absorption. These studies were potentially flawed as they studied healthy volunteers,[18] the volunteers were given larger doses of thyroxine than are normally prescribed, and they were also not on concurrent therapy for prolonged periods of time as is normal in clinical settings. Our study suggests that there is an interaction between PPIs and thyroxine.

PPIs may affect the absorption of thyroxine by increasing the pH of the stomach, but there is currently a paucity of conclusive evidence to substantiate this theory. Studies[21,22] have indicated that PPIs may interact with other drugs, such as clopidogrel, due to shared metabolism by cytochrome P450. The clinical significance of this interaction[23] is still not fully understood as many patients taking PPIs also have comorbidities. Studies into the mechanism of PPI interactions with thyroxine warrant further consideration as suboptimal dosing can exacerbate patient symptoms and quality of life, resulting in poor management of hypothyroidism. For 5·6% of patients concurrently taking thyroxine and a PPI, the interaction

is clinically significant, causing an increase in serum TSH of over 5 mU/l and placing them back into a biochemically hypothyroid state.

H2 receptor antagonists did not have a statistically significant effect on thyroxine absorption. This could be explained because the antagonists work by a different mechanism than PPIs. H2 antagonists also increase stomach pH, and this finding supports the likelihood that PPIs interact with thyroxine by mechanisms other than lowering stomach acidity. Glucocorticoids and DMARDs also did not cause a statistically significant change in TSH levels. This indicates that not all drugs affect thyroxine levels.

A 2011 study of (N = 41)[24] suggested statins did not have any effect on levothyroxine absorption, but patients were only followed for a period of 3 months. Interestingly, in this population-based study, statins caused a statistically significant decrease in serum TSH levels. Metformin has previously been shown to have this effect, but the mechanisms are unclear.[25,26] Further studies could examine whether metformin causes a statistically significant decrease in TSH in a large patient population in comparison with the decrease in TSH caused by statins. The mechanism of action causing this decrease could also be further investigated.

Suboptimal treatment can directly affect quality of life, and it may be important to monitor patients more closely when they are taking thyroxine and another drug is initiated, especially iron, calcium oestrogens or PPIs. Our study findings support the conclusion of other studies[16] that PPI therapy should be added to the list of medications affecting a patient's level of thyroid hormone in those patients being treated chronically with thyroxine.

For patients on long-term thyroxine, it may be best that it is swallowed either one hour before or four hours after food or concomitant iron and calcium[8,27] to ensure that thyroxine absorption is not affected by co-administration. This may also be the case for PPIs. If PPIs and oestrogen mainly affect thyroxine hepatic metabolism, then when these drugs are prescribed and a patient is on long-term thyroxine, the TSH needs to be carefully monitored with consideration to increasing the thyroxine dose.

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