Adverse Event Reporting in Patients with Thyroid Dysfunction Treated with Levothyroxine in Armenia. A Cross Sectional Pilot Study

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Abstract

Background and Aim. Currently two forms of levothyroxine are presented in pharmaceutical market of Armenia: Euthyrox and L-thyroxine. Local physicians have a choice of two different levothyroxine preparations, each of them with different dosage from 25 to 150mg. Oral levothyroxine (LT4) is the standard therapy for patients with hypothyroidism. The purpose of this report is to describe the adverse outcomes reported by endocrinologists, the frequent prescribers of levothyroxine, practicing in Armenia and to compare the rate of adverse reactions with data from different international research reports.

Materials and methods. A Pharmacovigilance questionnaire was developed based on the literature reports to assess potential adverse events attributable to the use of levothyroxine products. Statistical Analysis Results were collected, interpreted and presented as percentages.

Results. The study was with a cross-sectional design conducted in medical centers of Armenia using convenience sampling. The respondent parents of patients were selected using simple random sampling. Of the total 56 survey responses received, the majority 35 [63%] reported no adverse events. The adverse effects were due to new or unexpected symptoms in 2 (25%), a TSH change alone in 1 (12%), or both in 6 (75%). Most the symptoms (5/8 [65%]) were consistent with thyrotoxicosis, arrhythmias were documented in three cases, while 35% (3/8) of cases had symptoms typical of hypothyroidism.

Conclusions. Clinicians prescribing Euthyrox and L-thyroxine should be reminded that these products are from different manufacturers and patients/physicians should be made aware of all possible adverse reactions results, which could be different for these two products.

Keywords: levothyroxine, thyroid-stimulating hormone, hypothyroidism, oral levothyroxine

Introduction

Currently two forms of levothyroxine are presented in pharmaceutical market of Armenia: Euthyrox and L-thyroxine. Local physicians have a choice of two different levothyroxine preparations, each of them with different dosage from 25 to 150mg [1].

Oral levothyroxine (LT4) is the standard therapy for patients with hypothyroidism. Oral LT4 is available internationally in several formulations, including tablets, soft gel capsules and oral solution. Multiple brand-name and generic LT4 tablets are available. In the US, the

Food and Drug Administration (FDA) has developed a protocol for establishing bioequivalence of LT4 formulations based on serum thyroxine (T4) levels after a single oral dose administered to healthy volunteers [2]. This protocol has been criticized by professional endocrinology associations for ignoring serum thyroid-stimulating hormone (TSH) levels [3, 4]. There are concerns that the FDA's protocol could allow products with clinically significant differences in bioavailability to be declared therapeutically equivalent and interchangeable. Often, the substitution is made by the pharmacy without the physician's knowledge [5]. Even small differences between LT4

formulations can cause significant changes in TSH levels. This may be a particular concern in vulnerable populations, including elderly, pregnant, and pediatric patients [6, 7]. Problems that can be encountered when switching between formulations or when original products are reformulated include altered efficacy and adverse events, some of which can be caused by excipients. Patients should be maintained on the same LT4 preparation if possible. If the LT4 preparation is changed, TSH levels should be evaluated and, if necessary, the dose of LT4 adjusted [8-10].

The more common side effects of levothyroxine can include: increased appetite, weight loss, heat sensitivity, excessive sweating, headache, hyperactivity, nervousness, anxiety, irritability, mood swings, trouble sleeping, tiredness, tremors, muscle weakness, changes in menstrual periods, hair loss (usually temporary), diarrhea, vomiting and stomach cramps. If these effects are mild, they may go away within a few days or a couple of weeks. If they are more severe then patients need medical attention [11-14].

The purpose of this report is to describe the adverse outcomes reported by endocrinologists, the frequent prescribers of levothyroxine, practicing in Armenia and to compare the rate of adverse reactions with data from different international research reports [15, 16].

Materials and Methods

A Pharmacovigilance questionnaire was developed based on the literature reports to assess potential adverse events attributable to the use of levothyroxine products. We used a modified survey tool that was created to gather data similar to that used by FDA and developed by the American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES) to survey the experience of physicians caring for patients with thyroid disease on thyroid extract or LT4 therapy [17].

Participants of the study were patients with thyroid dysfunction who

sought therapy services in specialized departments. The study was with a cross-sectional design conducted in medical centers of Armenia using convenience sampling and included randomly selected endocrinology services in the district towns and in the capital city. We used convenience sampling model and not a randomized approach as not all regional hospitals in the country include endocrinology departments. The respondent parents of patients were selected using simple random sampling. A minimum sample size of 56 patients was derived using the formula $N = [z^2 p (1-p)] \div ME^2$ [18], where z = confidence interval at 95% thus 1.96; p = assumed prevalence of adverse reactions, 50%; and ME = margin of error, 0.05. Criteria for the inclusion in the study sample were the impaired level of TSH and/or thyroid hormones and confirmed diagnosis of thyroid disorder.

The questionnaire was distributed among endocrinologists working in different centers and the result of reports received from physicians were compared to international data reported from variety of authors. Following the development of the questionnaire we contacted the physicians in Armenian Canadian medical Center, Erebuni clinic, and Kotayk regional hospitals. A total of 14 responses were received between March 2021 and May 2021. The current report describes the adverse events reported by physicians caring for 56 individuals using thyroid formula Euthyrox or L-thyroxine.

Statistical Analysis Results were collected, interpreted and presented as mean and percentages. For statistical and graphical evaluations Microsoft Excel 2013 (Roselle, IL, USA) was used.

"N-1" Chi-squared test was used to compare the proportions registered in the local study and in previous reports.

The modified pharmacovigilance survey questionnaire [17] included 11 questions with subpoints.

	Questions
1.	The reason you suspect an adverse reaction to thyroid hormone is based upon:
	New Symptoms:
	Hyperthyroid symptoms –
	Hypothyroid symptoms –
	Palpitations –
	Palpitations –
	Difficulty sleeping –
	Nervousness –
	Weight loss –
	Weight gain –
	Dry skin –
	Constipation –
	Hair loss –
	Menstrual irregularities –
	Change in TSH despite no change in dosage –
	Both –
2.	Is your patient compliant with taking thyroid pills?
	Yes, I have asked the patient who says that pills are NOT or rarely missed –
	Yes, Verified by pill count/pharmacy records –
	Yes, I both asked the patient AND verified pill count/records –
	No-
3.	Has your patient been started on any of these medications since the last TSH? (These medications can inhibit absorption or metabolism)
	Select more than one as appropriate:
	Bile and acid binding resin (absorption) –
	Calcium (absorption) –
	Multivitamins (absorption) –
	Estrogen (BCP/HRT) –

	Iron (absorption) –
	Sucalfate (absorption) –
	Phenytoin (metabolism) –
	Rifampin (metabolism) –
	Not applicable –
4.	Is your patient pregnant?
	Yes –
	No, verbal confirmation (or male) –
	No, negative pregnancy test –
5.	Your patient is taking thyroid hormone for:
	Goiter or nodules –
	Hypothyroidism –
	Thyroid Cancer –
6.	The results of the most recent TSH was:
	Less than 0.1 –
	0.1 – 0.4 –
	0.5 – 1.9 –
	2 – 4.9 –
	5 – 9.9 –
	More than 10
7.	The results of the last TSH on record was:
	Less than 0.1 –
	0.1 – 0.4 –
	0.5 – 1.9 –
	2 – 4.9 –
	5 – 9.9 –
	More than 10 –
8.	Was the dose stable between the TSH measurements?
	No, not stable –
	Yes, stable –
9.	Was your patient given a different type of thyroid medication than you previously Prescribed?
	Change from brand to generic –
	Change from generic to brand v
	Change from one brand to another –
	Change from one generic to another generic –
	No change –
10.	If the type of preparation was changed, it was changed by:
	Not applicable --
	Pharmacy with knowledge –
	Pharmacy without your knowledge –
	You/your office –
11.	Did this change in the type of preparation result in any serious adverse events?
	Yes:
	Urgent Clinic Visit –
	Hospitalization –
	Missed work –
	Emergency Room Visit –

Table 1. *The questions and subpoints of the pharmacovigilance questionnaire*

Results

Of the total 56 survey responses received, the majority 35 [63%] reported no adverse events. A total of 21 completed adverse event (AE) reports (37% of total responses) were further reviewed. Of these, 12 (59%) reported adverse experiences with levothyroxine. Of the 12 patients reported, only 10 patients were on it as sole treatment for their thyroid disorder and among these 10 reports, 2 of the adverse events indicated that there had been recent dose adjustments which would account for the symptoms and altered thyroid function assessments.

All the reports were focused on adverse events observed by physicians caring for patients on thyroid hormone prescription. After elimination of

reports related to noncompliance with Euthyrox (11), erroneous reporting (4), interfering medication use (4), pregnancy (3), recent changes in levothyroxine dosing and the reporting of symptoms only associated with an unchanged TSH values (6), after these adjustments, 8 reports of adverse events remained.

Compliance with the levothyroxine treatment was confirmed by the reporting physician based on verbal report of the patient in 47/56 (84%) of the cases. Levothyroxine therapy was being administered for the indications of hypothyroidism in 48 of the 56 patients (86%), thyroid cancer in 2/56(3%), and goiter or nodule suppression in the remaining 6/56 (11%) report. Therefore, biochemical euthyroidism would have been

expected in 86% or more of the reports and TSH suppression of some degree would have been expected in the remaining cases.

Of the 56 completed pharmacovigilance reports on compliant individuals on stable doses of levothyroxine, the adverse effects were due to new or unexpected symptoms in 2 (25%), a TSH change alone in 1 (12%), or both in 6 (75%). Symptoms include both typical thyrotoxic symptoms (e.g., weight loss, nervousness, difficulty sleeping, palpitations, and tiredness) and typical hypothyroid symptoms (weight gain, constipation, menstrual irregularity, dry skin, fatigue and hair loss). Most the symptoms (5/8 [65%]) were consistent with thyrotoxicosis, arrhythmias were documented in three cases, while 35% (3/8) of cases had symptoms typical of hypothyroidism.

The TSH distribution from suppressed to elevated levels found during the survey is described in this figure. Prior to the reported adverse event, TSH values were within the normal range (0.5 to 5) in 4 of 8 (50%) of the reports, TSH was suppressed below normal in 3 of 8 (38%), and exceeded

the upper limit of the reference range in 1/8 (12%) TSH values reported. At the time of the reported adverse event, 6 of the 8 (75%) TSH values were below normal with 1 of 8 (12%) of TSH values were suppressed but detectable and the majority, 1 of 8 (12%) being undetectable.

The overall trend in TSH change at the time of the reported event was a substantial increase of the number of subjects demonstrating evidence of excess thyroid hormone (5/8) exposure a rate which nearly doubled.

Free text comments were made by 4 physicians during the survey. The most common reason cited for discontinuing the drug was an inability to dose the drug based on symptoms and TSH values (2 out of 4 comments). 1 of these 4 physicians stated that the drug was initially prescribed by a different provider. Arrhythmias were documented in two patients. The tables presented show the rate of adverse events collected in Armenia and compare them with data of international reports:

The reasons	N%	
	International data	Local report data
Both	68%	75%
New symptom	16%	25%
TSH Change	15%	12%

Table 2. The reason you suspect an adverse reaction to thyroid hormone extract is based upon:

Compliance confirmed N (%)		
	International data	Local report data
Verbally 76 (84)	84%	90%
Clinical records	16%	10%
Both	32%	24%

Table 3. Proportion of patients who are compliant with taking thyroid pill? (Only those answering yes included).

Symptoms Count (%)	Count (%)	
	International data	Local report data
Hyperthyroid	65%	75%
Hypothyroid	5%	12%
Not Specified	16%	N/A
Others. Palpitation, menstrual irregularities, constipation, sleep issues, hair loss	13%	13%

Table 4. Symptoms documented in patients

TSH range	Count (%)	
	International data	Local report data
<0.1	59%	75%
0.1-0.4	32%	12%
0.5-1.9	0%	0%
2-5	0%	0%
5-10	7%	10%
>10	2%	3%

Table 5. The results of the most recent TSH

Condition	Count (%)	
	International data	Local report data
Goiter or nodule	14%	11%
Hypothyroidism	84%	86%
Thyroid Cancer	2%	3%

Table 6. Disorders in patients administered with the hormone

Discussion

This survey of Levothyroxine documents 8 validated reports of adverse events accompanied by objective changes in the thyroid function that

were associated with the use of stable doses of the compound in compliant subjects.

The purpose of this pilot study was not only the assessment of adverse reactions registered in patients with thyroid disorder treated with Euthyrox and L-thyroxine, and estimation of the prevalence of these adverse effects. The study aimed to compare the rates with data available from the previous research reports. The tables presented in results reveal somewhat higher prevalence of adverse reactions in a previously reported study (32% vs 24%) [17]. The sample sizes compared were different (565 vs 56), but statistical comparison of results revealed no significant difference in proportions (Chi-squared = 1.515; P = 0.2184).

The sample size of this study was relatively small, also limiting the generalizability of our findings. There may also have been selection bias as the most dramatic cases seen would have been preferentially put forward as adverse events. However, since the reporting was voluntary and provided by practitioners, the frequency of adverse events was likely under-reported.

Although the manufacturers of levothyroxine have made great strides to standardize the content of their products, the preparations remain not fully controlled by the regulatory bodies. The responses documented in this survey raise clinical concerns. It is important to provide a broader understanding of issues that may arise from use of the Euthyrox and L-thyroxine among physicians, pharmacists, and patients to achieve optimal treatment for hypothyroidism. Clinicians prescribing Euthyrox or L-thyroxine should be reminded that these products are from different manufacturers and patients/physicians should be made aware of all possible adverse reactions results, which could be different for these two products. These data show that the frequency of dose adjustments in levothyroxine users appears to be much more common when compared to rates observed in different international reports. Most symptoms encountered in those using levothyroxine were consistent with exposure to excessive thyroid hormone use.

Conclusions

We have no evidence that the potency of levothyroxine preparations varies with currently available products: Euthyrox and L-thyroxine, nor that any such variability played any role in the events reported here. Further studies are required to compare the adverse events of Euthyrox and L-thyroxine with that of other levothyroxine preparations and assess the rate of these events to justify the continued use of selected preparations.

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