

Analysis of spontaneously reported adverse drug reactions of levothyroxine in Croatia

Koppmann, Ellen Sophie

Master's thesis / Diplomski rad

2019

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet**

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:171:657601>

Rights / Prava: [In copyright](#)/[Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-11-22**



Repository / Repozitorij:

[MEFST Repository](#)



**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

Ellen Sophie Koppmann

**ANALYSIS OF SPONTANEOUSLY REPORTED ADVERSE DRUG
REACTIONS OF LEVOTHYROXINE IN CROATIA**

Diploma thesis

Academic year:

2018/2019

Mentor:

Prof. Darko Modun, MD, PhD

Split, October 2019

Table of Contents

1. INTRODUCTION	1
1.1. Thyroid gland physiology	2
1.1.1. Synthesis of thyroid hormones	2
1.1.2. Transport and metabolism of thyroid hormones.....	2
1.1.3. Mechanism of action of thyroid hormones.....	3
1.1.4. Physiologic effects of thyroid hormones	3
1.1.5. Regulation of thyroid hormone secretion.....	4
1.2. Thyroid gland pathophysiology.....	4
1.2.1. Hypothyroidism.....	4
1.2.1.1. Epidemiology	5
1.2.1.2. Etiology	5
1.2.1.3. Clinical presentation.....	6
1.2.1.4. Diagnosis	6
1.3. Treatment of hypothyroidism - levothyroxine.....	7
1.3.1. History	7
1.3.2. Mechanism of action	7
1.3.3. Pharmacokinetics	7
1.3.4. Indications and dosage.....	8
1.3.5. Contraindications	8
1.3.6 Adverse drug effects.....	8
1.3.7 Current issues and new treatment approaches	8
2. OBJECTIVES.....	1
3. SUBJECTS AND METHODS	12
4. RESULTS	12
5. DISCUSSION	16
6. CONCLUSION	20
7. REFERENCES.....	23
8. SUMMARY	29
9. CROATIAN SUMMARY.....	31
10. CURRICULUM VITAE.....	33

First of all, I would like to express my deep gratitude to my mentor Prof. Darko Modun, MD, PhD for offering the possibility to finish this chapter of my life. I would like to thank Josipa Bukić, MPharm for her help and guidance throughout the process of writing.

I also want to thank Assist. Prof. Joško Božić, MD, PhD for his assistance.

The past six years would not have been possible without the love and support of my family and friends. I appreciate every message you sent, every phone call you made and every journey you took to Split to visit me.

To my parents, thank you for your continuous support in everything I do and giving me the chance to pursue my dream of being a doctor. To my sister, thank you for always having my back and making me laugh.

Anna and Theresa, thank you for being the best friends I ever could have wished for, 20 years and counting. And to the friends I made in Split, thank you for filling my time here with moments I will gladly look back on.

1. INTRODUCTION

1.1. Thyroid gland physiology

The thyroid gland is an endocrine organ located in the anterior neck which produces several hormones that greatly influence the body's metabolism (1). The major thyroid hormones thyroxine (T4) and triiodothyronine (T3) directly affect the metabolic rate, therefore playing an important role in growth and development of infants and children as well as in regulation of body temperature and energy levels in adults (2). The gland secretes another hormone, calcitonin, which is involved in calcium metabolism but will not be further discussed here (1).

1.1.1. Synthesis of thyroid hormones

Necessary for the synthesis of thyroid hormones is the adequate oral intake of iodide in the form of iodine. Recommended daily intake for adults is 150 mcg, for pregnant women it is 200 mcg (2). The first step in thyroid hormone synthesis is the uptake and concentration of iodide from the circulation into the thyroid cells by a process called "iodide trapping", a type of active transport stimulated by thyroid-stimulating hormone (TSH) (1,3).

The enzyme thyroidal peroxidase then oxidizes the iodide into iodine which enters the colloid and is bound to tyrosine molecules of thyroglobulin, a protein formed in the thyroid cells. After several stages of iodination of tyrosine, the final hormonal products thyroxine (which makes up the majority) and triiodothyronine remain bound to thyroglobulin and can be stored in this form for several months (1,3).

1.1.2. Transport and metabolism of thyroid hormones

In order for T4 and T3 to be released from the thyroid gland into the circulation, they first must be cleaved from thyroglobulin by a process of exocytosis and proteolytic cleavage of thyroglobulin (2). Much more T4 than T3 is synthesized and therefore released (93% vs 7%), but over the course of a few days, about half of the T4 is slowly deiodinated to T3 (1).

In the plasma, both hormones are mostly bound to plasma proteins such as thyroxine-binding protein, transthyretin and albumin (3). Comparing the two hormones, slightly more T4 (99.98%) is protein-bound and it has a longer biological half-life of 6 to 7 days. 99.8% of T3 is protein-bound and it not only acts more rapidly and has a shorter half-life of 30 hours but is also three to five times more potent on a molar basis (3). The portion of both unbound hormones in plasma is physiologically active: It is available for uptake by tissues and also participates in the feedback loops that regulate thyroid hormone synthesis and secretion (3-5).

In the tissues, thyroid hormones are metabolized by deiodination. T₄ is deiodinated either into the metabolically active T₃ or the metabolically inactive reverse triiodothyronine (rT₃). Both T₄ and T₃ are conjugated to glucuronides in the liver and then excreted in the bile. In the intestines, the conjugates are hydrolyzed and then either reabsorbed or excreted in the stool (3).

1.1.3. Mechanism of action of thyroid hormones

Thyroid hormones exert their effect by activating transcription of a wide variety of genes leading to a generalized increase of functional activity throughout the entire body (1). As stated before, upon entering the cells of different body tissues most of the T₄ is transformed into T₃. T₃ can then enter the cell nucleus, bind to specific T₃ receptor proteins and thereby activate formation of RNA and protein synthesis. This is a complex process that takes time and explains partly why effects of thyroid hormone supplementation are not immediately visible (2).

On the other hand, some effects of thyroid hormones on a molecular level appear much faster and cannot be explained by changes in protein synthesis. These so-called “non-genomic” cellular effects have been shown in some tissues such as the heart and pituitary gland and seem to be mediated by regulation of ion channels, activation of intracellular secondary messenger systems and many other mechanisms (1,3).

1.1.4. Physiologic effects of thyroid hormones

Already during fetal development, thyroid hormones play an important role by promoting growth and development of the brain. This continues throughout the first years of life and in addition to that, thyroid hormones promote general growth and skeletal development as well (1).

Thyroid hormones increase the basal metabolic rate by increasing the metabolism in almost all cells of the body: carbohydrate, fat and protein metabolism are stimulated (1). On the heart, the hormones exert chrono- and inotropic effects by increasing number and affinity of beta-adrenergic receptors, enhancing the response to circulating catecholamines and increasing the proportion of alpha-myosin heavy chains (3).

Other effects include increased respiration and gut motility as well as excitatory effects on the central nervous system. They also affect other endocrine glands, not only by increasing rates of secretion of certain hormones but also by increasing tissue needs. For example, an increase in glucose metabolism calls for increased insulin secretion (1). Other

instances of thyroid hormone influence become more evident when they are disordered, as is seen with irregular menstrual bleeding and cycles when there is an excess or lack in thyroid hormones (1,6).

1.1.5. Regulation of thyroid hormone secretion

The secretion of thyroid hormones is regulated by specific feedback mechanisms. The hypothalamus releases thyrotropin-releasing hormone (TRH) which stimulates the anterior pituitary gland to release TSH which in turn stimulates the release of T4 and T3 by the thyroid gland (3). TSH exerts its effect via several mechanisms: it increases the rate of iodide trapping, increases iodination of tyrosine, increases size and number as well as secretory activity of thyroid cells and it increases proteolysis of the already stored thyroglobulin. While this last effect only takes minutes to show, the others need more time (hours to weeks) to completely develop (1).

In turn, free T4 and T3 inhibit TSH secretion by the anterior pituitary in two ways: they act directly on the anterior pituitary and indirectly by inhibiting TRH secretion by the hypothalamus (3). Several other factors have been shown to inhibit TSH secretion, for example stress, dopamine and changes in temperature of the surroundings (3). In recent years, this model of regulatory feedback loops has been expanded and researchers now assume that it is much more complex. For example, it is now suggested that non-classic thyroid hormones such as reverse triiodothyronine (rT3) may act as modulators of feedback regulation as well (5).

1.2. Thyroid gland pathophysiology

Diseases of the thyroid gland can be broadly classified in five categories: hypothyroidism, due to a deficiency of thyroid hormones; hyperthyroidism, due to an excess of thyroid hormones; goiter, meaning a diffusely enlarged thyroid gland due to prolonged elevation of TSH; thyroid nodule, referring to a focal enlargement of the thyroid due to either a benign or malignant process; and finally abnormal thyroid function tests in an otherwise healthy person (3).

1.2.1. Hypothyroidism

Hypothyroidism is a very common disorder and refers to all pathological conditions defined by a deficiency in thyroid hormones T4 and T3. Since the clinical presentation is very

varied and symptoms are often non-specific, the main definition of hypothyroidism is biochemical (6).

1.2.1.1. Epidemiology

As definitions and diagnostic criteria differ between countries, reports of prevalence of hypothyroidism worldwide vary (6). A meta-analysis in 2014 analyzed epidemiologic data from European countries and found that the total prevalence of hypothyroidism was 3% and the prevalence of undiagnosed hypothyroidism almost 5%. Moreover, 80% of the cases of undiagnosed hypothyroidism were subclinical (7). Hypothyroidism is much more common in women than men and in people older than 65 years (4,6,7).

1.2.1.2. Etiology

The majority of hypothyroidism is “primary” hypothyroidism, meaning that there is a deficiency of thyroid hormones themselves and not TSH or TRH (6). Worldwide, the most common cause of hypothyroidism is iodine deficiency (4). While a part of Europe still is mildly iodine deficient, many countries have implemented successful programs of iodine supplementation (8). On the other end of the spectrum, studies have shown that an excess iodine intake can be related to hypothyroidism as well (9).

In regions of adequate iodine supply, chronic autoimmune thyroiditis (Hashimoto’s thyroiditis) is the main cause of hypothyroidism (4). This disease is characterized by formation of autoantibodies against thyroid peroxidase (TPO) and thyroglobulin (Tg) which leads to glandular inflammation and later on fibrosis (3,10). More women than men suffer from Hashimoto’s and while there have been discoveries relating to underlying genetic mechanisms and external influencing factors in the recent past, this is a phenomenon that so far cannot be explained completely (10).

Iatrogenic hypothyroidism is also common (4). Treatment for hyperthyroidism or thyroid cancer in the form of radioiodine treatment, surgical removal of the gland or neck radiation typically leads to hypothyroidism (6). Drugs used in the treatment of other diseases such as Amiodarone or Lithium can also cause hypothyroidism (12,13). Central hypothyroidism (also called secondary or tertiary hypothyroidism) is caused by disorders of the anterior pituitary gland or hypothalamus that have in common insufficient TSH stimulation of a healthy thyroid gland. This form is rarer and does not show the female prevalence observed with other types of hypothyroidism (6,14).

1.2.1.3. Clinical presentation

The clinical presentation of hypothyroidism has a wide range, depending not only on severity but also on other factors such as age and gender. For example, it has been shown that individuals older than 60 years report less symptoms related to hypothyroidism than those younger than 50 years (11). In addition, the onset of symptoms is often insidious and goes unnoticed (4). Patients most commonly complain about tiredness, lethargy, weakness and cold intolerance. They may notice dry skin and hair loss and find it difficult to concentrate. Other symptoms are weight gain despite decreased appetite, constipation, dyspnea, a hoarse voice and paresthesia. Female patients may notice changes in their menstrual cycle, ranging from menorrhagia to oligo- or amenorrhea (4,6).

On physical examination, hypothyroid patients often show a round puffy face with periorbital edema as well as peripheral edema. Their skin is dry, cold and brittle and diffuse alopecia may be present. Other findings include bradycardia, delayed tendon reflex relaxation, serous cavity effusions and depression (3,4).

The most severe form of hypothyroidism and a medical emergency is myxedema coma. It is characterized by an altered mental state (but not necessarily the state of coma) and biochemical alterations (such as hyponatremia, hypoglycemia) in addition to the other features of hypothyroidism. It can either be the first presentation of hypothyroidism or appear in patients who are only partially treated or exposed to some type of additional stress, for example sepsis (15).

1.2.1.4. Diagnosis

The first step in diagnosis of hypothyroidism is usually measurement of TSH (4). In overt primary hypothyroidism, TSH will be increased ($>10\text{mIU/L}$) and free (unbound) T4 will be decreased (16). The etiology can then be further assessed by testing for the presence of thyroid autoantibodies and in some cases, an ultrasound and/or fine needle aspiration might be necessary (4).

In the case of subclinical hypothyroidism, TSH is elevated but levels of free T4 are normal (16,17). The European Thyroid Association classifies subclinical hypothyroidism as either mild (TSH $4.0\text{-}10.0\text{mIU/L}$) or severe (TSH $>10.0\text{mIU/L}$), whereas the mild type is more common (18). It is important to consider the patient's age when analyzing thyroid function test results because the reference range of normal TSH values seems to widen with increasing age, meaning that a mild increase of TSH in a patient older than 65 years might be physiological and not a sign of subclinical hypothyroidism (16-18). If upon first investigation

for hypothyroidism TSH is within reference range, primary hypothyroidism can be ruled out and pituitary function should be investigated next (4).

1.3. Treatment of hypothyroidism - levothyroxine

1.3.1. History

Although levothyroxine (LT4) was first synthesized as a T4 replacement in 1926, at that time desiccated animal thyroid extract preparations were more popular for treatment of hypothyroidism. But in the 1960s, it had become clear that levothyroxine was far more superior due to its consistency in content and lack of allergenic foreign proteins (2,19). Another advantage was the discovery that in the body, T3 is generated by peripheral conversion from levothyroxine, so that preparations no longer needed to contain additional T3 which was related to most of the adverse effects due to its pharmacokinetic profile (2,20,21).

Today, levothyroxine is one of the most prescribed drugs worldwide and recommended by all treatment guidelines as the first and main choice in therapy of hypothyroidism (6,16,21). It is available in different formulations and generic forms: powders for intravenous solutions, tablets, soft gel capsules and oral solutions (22).

1.3.2. Mechanism of action

As levothyroxine is the synthetic equivalent of T4, it undergoes the same processing and has the same mechanism of action (2). In recent years though the traditional concept of peripheral levothyroxine conversion has been challenged and it has been suggested that the rate of conversion into T3 might be lower in individuals who must rely on synthetic hormone which would lead to decreased efficacy of the drug (21).

1.3.3. Pharmacokinetics

Levothyroxine is absorbed mostly in the small intestine. Certain foods (e.g. coffee, soy) and drugs (e.g. ciprofloxacin, proton pump inhibitors) can impair its absorption so it is recommended to take the daily dose of levothyroxine in the morning, 30 to 60 minutes before breakfast (2,6). Bioavailability is 60 to 80% in euthyroid individuals but might be slightly higher in the hypothyroid (22). The time to maximum concentration is slightly longer in hypothyroid individuals with 3 versus 2 hours in euthyroid persons (22). The long half-life of 7 days permits once-daily dosing (2). Various conditions such as renal or hepatic impairment alter the pharmacokinetic properties of levothyroxine (22).

1.3.4. Indications and dosage

The major indication is hormone replacement therapy in all types of overt hypothyroidism, and additionally it is used in treatment of euthyroid goiters as well as an adjunct in treatment of thyroid cancer (2,22). The indications for treatment of subclinical hypothyroidism are not as clear and more controversial, especially with regard to the patient's age, the subjective feeling of symptoms and biochemical degree of subclinical hypothyroidism (4,16,18,23).

The dose is generally based upon weight (1.6 or 1.7 mcg/kg body weight/day in an adult, typically 100–150 mcg/day) and might need to be adjusted according to the amount of residual thyroid function, age of patient and etiology of hypothyroidism (2,4,21). In the elderly population, those with longstanding disease and those with preexisting heart conditions the starting dosage should be lower due to effects on the heart (2). In all patients the treatment should be followed up closely by checking TSH and free T4 in regular intervals so that levothyroxine dosage can be adjusted accordingly (2,4). Relief of symptoms may take up to six months after TSH levels have normalized (4).

1.3.5. Contraindications

There are only few contraindications to treatment with levothyroxine. It should not be given in any kind of thyrotoxicosis, the early phase of acute myocardial infarction, untreated adrenal insufficiency and known hypersensitivity to levothyroxine (16,21).

1.3.6 Adverse drug effects

Levothyroxine is generally assumed to have a favorable safety profile. Most adverse drug effects are related to overtreatment leading to exogenous thyrotoxicosis (24). These adverse effects can be cardiovascular (palpitations, tachycardia, atrial fibrillation), neurologic/psychiatric (restlessness, increased nervousness, insomnia) and heat intolerance. Chronic overtreatment has been related to decreased bone density (2,16,24).

1.3.7 Current issues and new treatment approaches

Over the past years, critical evaluation of the standard diagnostic and treatment parameters of hypothyroidism has increased. The use of TSH as the main focus of diagnosis and guide for treatment success is increasingly criticized (18,19). Definition and necessity of treatment of subclinical hypothyroidism are complex topics and controversial (17,18,23).

Additionally, there is a group of patients that is not satisfied with treatment results of levothyroxine monotherapy (18-21). They report persistence of symptoms of hypothyroidism despite being in the optimum range of treatment biochemically (6). In those cases, it is recommended to check for concurrent diseases and issues in drug adherence as a cause first (6,25,26). But this group of patients may also seek treatment with a combination therapy of levothyroxine and liothyronine (LT3) which is supported by some physicians despite inconclusive study results on its questioned superior effectiveness so far (6,16,20,27,28). In the future, treatment of hypothyroidism will probably become more personalized (29).

1.4. Pharmacovigilance

Pharmacovigilance is defined by the World Health Organization as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” (30). The WHO established its own Programme for International Drug Monitoring in the 1960s and today, the majorities of countries have their own national pharmacovigilance systems and participate in transnational operations such as the EU pharmacovigilance system (30-32).

The term adverse drug reaction is used to describe harmful or unpleasant reactions caused by intervention with a medicinal product (33). Adverse drug reactions vary in severity from “non-serious” when reactions are transient and can be managed without hospitalization to “serious” when they lead to death, a general life-threatening situation, (prolonged) hospitalization, persistent or significant disability, congenital anomalies or birth defects, or some other important medical condition (34). For patients themselves, even adverse drug reactions that are classified medically as “non-serious” can still be an issue as they negatively impact their quality of life and may lead to problems in drug adherence (35). In the European Union, studies estimate that 3.5 to 5% of hospital admissions are caused by adverse drug reactions and that around 10% of patients who are already hospitalized will experience an adverse drug reaction which in total leads to societal costs of up to €79 billion (32,36).

Reporting of adverse drug reactions in the post-marketing stage of drugs is of great importance for drug safety. Due to the standard design of randomized controlled trials for a new drug, only a limited number of people with certain characteristics can be investigated. Usually less than 5000 individuals have been exposed to a new drug when it is released to the market which means that only the most common adverse drug reactions can be found. The analysis of adverse drug reaction reports therefore offers information on rare and very rare adverse drug reactions as well as effects of long-term use (37). In addition, the effects of

drugs on groups of people that normally cannot be easily enrolled into clinical trials such as pregnant women and elderly people can be studied (34). Because elderly people often have several comorbidities and need to take a variety of different drugs, they commonly experience adverse drug reactions caused by complex drug-to-drug interactions (34,38).

One major issue encountered in voluntary reporting systems is the underreporting of adverse drug reactions with estimates saying that only 5 to 10% of adverse drug reactions are reported (34,39). A systematic review by Varallo *et al.* in 2014 found the main reasons why health care professionals did not report adverse drug reactions to be ignorance, insecurity and indifference (39). Another study observed that some adverse drug reactions are considered to be too common, mild or complex to report (40). To increase reporting rates, education of health care professionals regarding pharmacovigilance should be improved and the reporting of adverse drug reactions at patient-level increased (35,39,40).

2. OBJECTIVES

To analyze levothyroxine adverse drug reactions reported to Agency of medicinal products and medical devices of Croatia. The hypotheses are:

1. The highest number of levothyroxine adverse drug reaction reports will be in 2018.
2. The most frequent reporter qualification in the present study will be pharmacists.

3. SUBJECTS AND METHODS

This was a retrospective study containing data on reported adverse drug reactions which have been collected by the Agency of Medicinal Products and Medical devices of Croatia (HALMED). Data on adverse drug reaction reports provided by HALMED was extracted from the pharmacovigilance database VigiBase.

In the present study, the drug studied was levothyroxine, formulated as oral tablets. This active substance in particular drug formulation has been marketed in Croatia as three different trade names during the examined period, and all of them were included in the study. The examined period was from January 2006 to 31 December 2018.

The following data of adverse drug reaction reports were analyzed: qualification of the reporters (pharmacist, physician, consumer/non health professional and other health professional), patients' gender and age (infant, child, adolescent, adult, elderly), seriousness according to one of the following criteria (caused/prolonged hospitalization, disabling, life threatening, other and death), number of other drugs used in therapy and classification according to Medical Dictionary of Regulatory Activities (MedDRA). Adverse drug reactions could be classified in 27 System Organ Classes (SOCs). Furthermore, they could be represented in more than one SOC and grouped by different classifications (e.g., by etiology or manifestation site).

The data provided by HALMED was coded using Microsoft Office Excel 2016 and descriptive statistical analysis was performed subsequently. Results are presented as whole numbers and proportions, where appropriate. Statistical analysis was performed using MedCalc software for Windows (v.11.5.1.0, MedCalc Software, Ostend, Belgium) and Chi square test was used for comparing categorical variables. The significance level was set at $P < 0.05$.

4. RESULTS

In the period from 2006 to 2018, HALMED obtained 146 adverse drug reaction reports for levothyroxine. The number of reports in each year is presented in Figure 1. The number of reports has increased in the examined period, with the largest proportion being reported in 2018, specifically 33 adverse drug reaction reports, which stands for 22.76% of all reports.

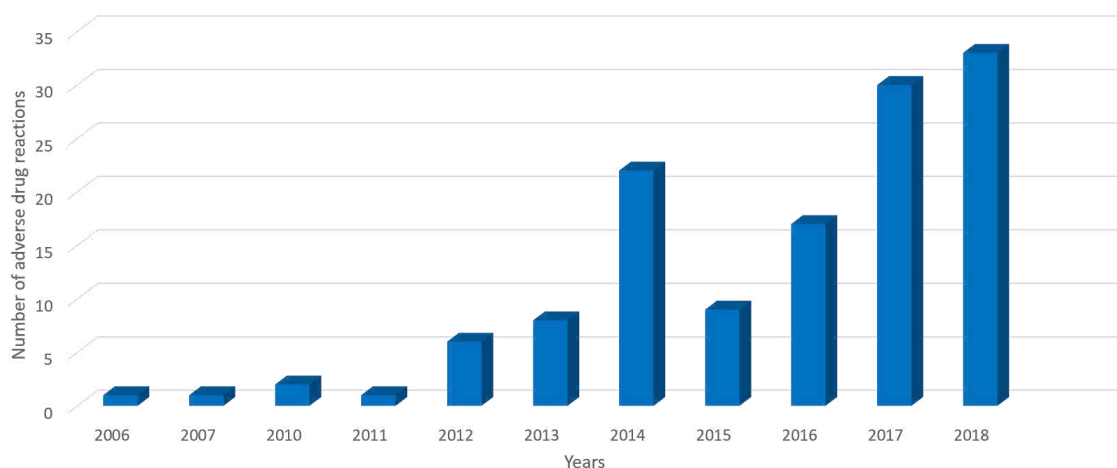


Figure 1. Number of levothyroxine adverse drug reactions through the years

Patients who experienced adverse drug reaction were mainly of female gender, 121 vs. 22 male patients, $P < 0.001$. The majority of them, 109 (75.2%), did not use any other concomitant drug. However, 2 reports (1.4%) included patients that used alarmingly high number of 17 drugs. Furthermore, the age group most commonly involved in the reports was adults, nearly 60% of reports. The proportion of all age groups is presented in Table 1.

Table 1. Levothyroxine adverse drug reactions patients age group

Age group	N (%)
infant	22 (15.7)
child	8 (5.7)
adolescent	7 (5.0)
adult	83 (59.3)
elderly	15 (10.7)
missing	10 (7.2)

Reporter qualifications that were included in majority of reports were pharmacists with 64 reports, and physicians with 57 reports. Distribution of reporter qualification per year is presented in Figure 3.

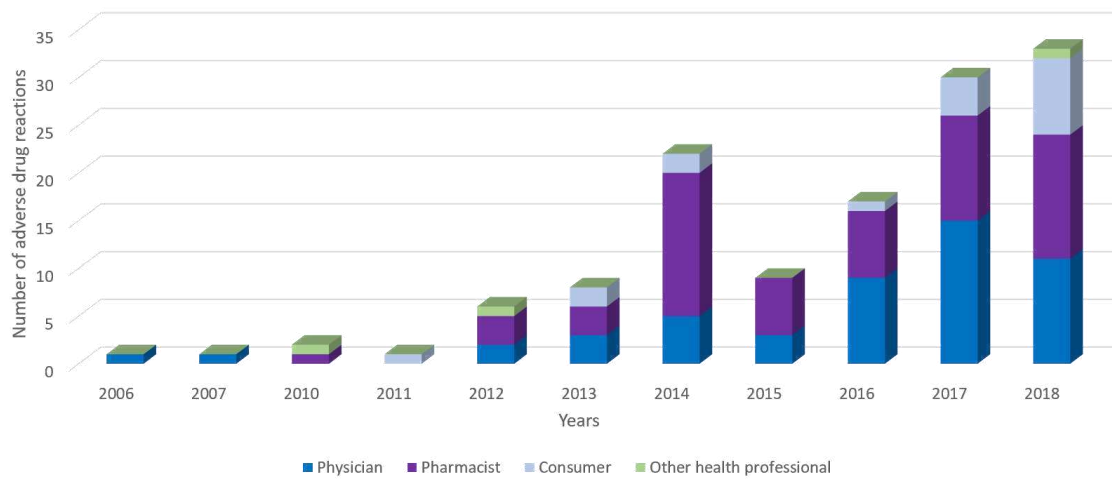


Figure 3. Distribution of reporter qualification through years

Distribution of all reports by seriousness is presented in Figure 4. Almost 75% of reports were classified as not serious.

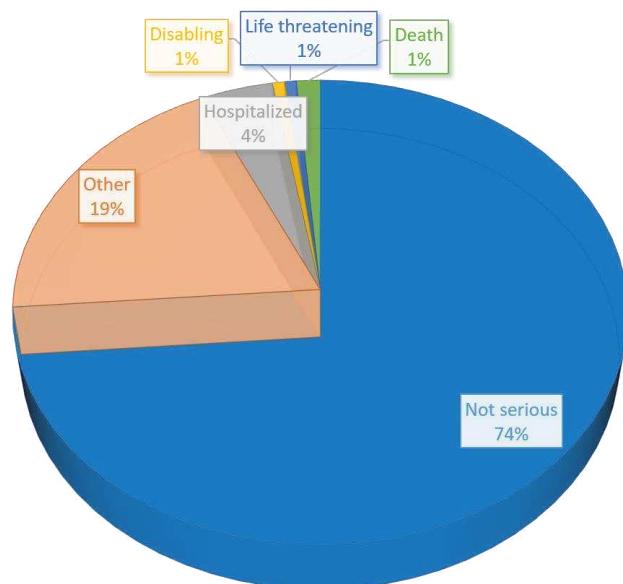


Figure 4. Distribution of levothyroxine adverse drug reaction reports by seriousness

System organ classes most commonly involved in levothyroxine adverse drug reactions were Injury, poisoning and procedural complications, General disorders and administration site disorders and Gastrointestinal disorders with 16.9%, 15.3% and 11.2% of the reactions respectively.

Table 2. System organ classes involved in levothyroxine adverse drug reactions

Class	N (%)
I. Blood and lymphatic system disorders	2 (0.8)
II. Cardiac	24 (9.9)
V. Endocrine disorders	2 (0.8)
VI. Eye disorders	1 (0.4)
VII. Gastrointestinal disorders	27 (11.2)
VIII. General disorders and administration site disorders	37 (15.3)
X. Immune system disorders	8 (3.3)
XI. Infections and infestations	1 (0.4)
XII. Investigations	3 (1.2)
XIII. Injury, poisoning and procedural complications	41 (16.9)
XIV. Metabolism and nutrition disorders	4 (1.7)
XV. Musculoskeletal and connective tissue disorders	7 (2.9)
XVII. Nervous system disorders	21 (8.7)
XIX. Product issues	1 (0.4)
XX. Psychiatric disorders	22 (9.1)
XXI. Renal and urinary disorders	2 (0.8)
XXII. Reproductive system and breast disorders	3 (1.2)
XXIII. Respiratory, thoracic and mediastinal disorders	3 (1.2)
XXIV. Skin and subcutaneous tissue disorders	26 (10.7)
XXV. Social circumstances	1 (0.4)
XXVI. Surgical and medical procedures	1 (0.4)
XXVII. Vascular disorders	5 (2.1)
Total	242 100

5. DISCUSSION

During the examined period, pharmacists were the most commonly involved in adverse drug reaction reporting practice for levothyroxine. This finding could be explained due to the fact that levothyroxine as a prescription only drug is prescribed on repeatable prescription. In Croatia this kind of prescription is prescribed by physician and patients can take the drug each month for the next 6 months, without the need of seeking the physician's assistance. Therefore, there is a reasonable premise that a patient taking his chronic therapy will not seek the physician's advice for the next 6 months, and pharmacists, as the most accessible health care professionals, have the opportunity to hear all patients' therapy problems or ask themselves each patient about any adverse drug reactions.

Adverse drug reaction reports for levothyroxine were previously studied in the United States (US). In the US, levothyroxine is one of the three most commonly prescribed drugs, estimated to be prescribed to 16 million individuals in 2013. Out of all drug prescriptions in the US, 88% are of generic drugs so it can be assumed that the vast majority of levothyroxine prescriptions is of generic type as well. A study by Marimuthu *et al.* analyzed the patient-relevant outcomes associated with generic levothyroxine preparations, among others. For generic levothyroxine, 67 case reports to the US Food Drug Administration (FDA) Adverse Event Reporting System (FAERS) were included. 77% of the reports were obtained from consumers and these were mostly women and had a median age of 56 years (41,42). In our study female gender was also most represented, however the consumers were not as engaged in the reporting practice as in the US study.

Furthermore, in the same study, the majority (64%) of reports could be mapped to the domain of physical health, as they were related to pain, fatigue, urinary and sleep disturbances. Interestingly, 11% of the reports were mapped to the domain of mental health being related to anxiety and depression, including completed suicide, while only 1% was mapped to social health. Notably, 24% of adverse drug reactions were unclassifiable, either because they were not patient-relevant or had incomplete data, indicating that MedDRA terms may not fully describe all patient-relevant outcomes (42). In our study the nervous system was not within the most commonly reported system organic classes, contrary to the US study.

In our study only oral tablets levothyroxine were included. However, future treatments to improve patient outcomes have been proposed. One possibility is the development of sustained release preparations of liothyronine. Two crossover trials on liothyronine monotherapy showed that a dosing regimen of liothyronine three times a day can achieve steady hormone and TSH levels but is difficult for patients to adhere to, especially in a

chronic disease. The other and more promising direction in the author's opinion is the field of stem cell research, specifically the creation of functioning thyroid follicles (42).

Until these goals can be reached, however, one rather effective and inexpensive possibility to optimize patient results on levothyroxine monotherapy could be to improve medication adherence. A study by Scavone *et al.* investigated the benefits of levothyroxine oral solutions and soft gel capsule formulations by analyzing 21 clinical studies (43). They found that these preparations had no relevant interactions with food, drinks and other medications, could be given to patients with gastrointestinal comorbidities and showed otherwise bioequivalence to the tablet form of levothyroxine. It was shown that compliance of patients was increased when they could take their medication with breakfast and that clinicians could use the different available dosages to individualize treatment of each patient, in total leading to better adherence and more stable TSH levels (43).

Main limitations of all studies in which adverse drug reaction reports are included are underreporting and deficiency of consumption data. The data, which would include both the number of individuals who consumed a particular drug, and the exact number of their experience of adverse drug reactions, would be beneficial for further risk calculations. Future studies on levothyroxine should gather both aforementioned data. However, the presented study analyzed previous reports and has some interesting findings considering levothyroxine adverse drug reaction reports data.

6. CONCLUSION

1. During the period from 2006 to 2018, the total number of levothyroxine adverse drug reaction reports was 146.
2. In the year 2018, 22.76% of all reports were obtained.
3. Female gender reported adverse drug reactions predominantly, 121 vs. 22 reports.
4. In 75.2% of reports the only drug involved was levothyroxine.
5. Pharmacists most commonly reported adverse drug reactions with 64 reports.
6. Injury, poisoning and procedural complications, General disorders and administration site disorders and Gastrointestinal disorders with 16.9%, 15.3% and 11.2% of the reactions respectively were most commonly reported system organ classes.

7. REFERENCES

1. Hall JE. Thyroid Metabolic Hormones. In: Hall JE, Guyton AC. Guyton and Hall Textbook of Medical Physiology. Philadelphia, PA: Saunders/Elsevier; 2010. p. 907-19.
2. Dong BJ, Greenspan FS. Thyroid & Antithyroid Drugs. In: Katzung BG, Masters SB, Trevor AJ. Basic & Clinical Pharmacology. New York:McGraw-Hill Medical;2012. p. 681-96.
3. Bauer DC, McPhee SJ. Thyroid disease. In: Hammer GD, McPhee SJ, editors. Pathophysiology of disease: An Introduction to Clinical Medicine. New York:McGraw-Hill Medical;2014. p. 571-91.
4. Jameson JL, Weetman AP. Disorders of the thyroid gland. In: Longo L, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo JL, editors. Harrison's principles of internal medicine. McGraw-Hill Professional;2011. p.2911-39.
5. Hoermann R, Midgley JEM, Larisch R and Dietrich JW. Homeostatic Control of the Thyroid–Pituitary Axis: Perspectives for Diagnosis and Treatment. Front Endocrinol (Lausanne). 2015;6:177.
6. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017;(17)30703-1.
7. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis. J Clin Endocrinol Metab. 2014;99(3):923-31.
8. Lazarus JH. Iodine status in europe in 2014. Eur Thyroid J. 2014;3(1):3-6.
9. Zimmermann MB. Iodine Deficiency. Endocr Rev. 2009;30(4):376-408.
10. Effraimidis G, Wiersinga WM. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. Eur J Endocrinol. 2014;170(6):R241-52.
11. Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Andersen S, Laurberg P. Hypothyroid symptoms fail to predict thyroid insufficiency in old people: a population-based case-control study. Am J Med. 2016;129(10):1082-92.
12. Zhong B, Wang Y, Zhang G, Wang Z. Environmental Iodine Content, Female Sex and Age Are Associated with New-Onset Amiodarone-Induced Hypothyroidism: A Systematic Review and Meta-Analysis of Adverse Reactions of Amiodarone on the Thyroid. Cardiology. 2016;134(3):366-71.

13. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet*. 2015;386(9992):461-8.
14. Persani L. Central Hypothyroidism: Pathogenic, Diagnostic, and Therapeutic Challenges. *J Clin Endocrinol Metab*. 2012;97(9):3068–78.
15. Beynon J, Akhtar S, Kearney T. Predictors of outcome in myxoedema coma. *Crit Care*. 2008;12(1):111.
16. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI et al. Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18(6):988-1028.
17. Gourmelon R, Donadio-Andréi S, Chikh K, Rabilloud M, Kuczewski E, Gauchez A et al. Subclinical Hypothyroidism: is it Really Subclinical with Aging?. *Aging Dis*. 2019;10(3):520–9.
18. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J*. 2013;2(4):215-28.
19. Midgley JEM, Toft AD, Larisch R, Dietrich JW, Hoermann R. Time for a reassessment of the treatment of hypothyroidism. *BMC Endocr Disord*. 2019. doi:10.1186/s12902-019-0365-4.
20. Hennessey JV, Espaillet R. Current evidence for the treatment of hypothyroidism with levothyroxine/levotriiodothyronine combination therapy versus levothyroxine monotherapy. *Int J Clin Pract*. 2018;72(2):e13062.
21. Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Individualised requirements for optimum treatment of hypothyroidism: complex needs, limited options. *Drugs Context*. 2019;8:212597.
22. Colucci P, Yue CS, Ducharme M, Benvenga S. A Review of the Pharmacokinetics of Levothyroxine for the Treatment of Hypothyroidism. *Eur Endocrinol*. 2013;9(1):40-7.
23. Calsolaro V, Nicolai F, Pasqualetti G, Calabrese AM, Polini A, Okoye C et al. Overt and Subclinical Hypothyroidism in the Elderly: When to Treat?. *Front Endocrinol (Lausanne)*. 2019;10:177.
24. Mammen JS, McGready J, Oxman R, Chia CW, Ladenson PW, Simonsick EM. Thyroid Hormone Therapy and Risk of Thyrotoxicosis in Community-Resident Older

- Adults: Findings from the Baltimore Longitudinal Study of Aging. *Thyroid*. 2015;25(9):979-86.
25. Kumar R, Shaukat F. Adherence to Levothyroxine Tablet in Patients with Hypothyroidism. *Cureus*. 2019;11(5):e4624.
 26. Cappelli C, Castello R, Marini F, Paoletta A, Marchetti M, Saullo M et al. Adherence to Levothyroxine Treatment Among Patients With Hypothyroidism: A Northeastern Italian Survey. *Front Endocrinol (Lausanne)*. 2018;9:699.
 27. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MPJ. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. *Eur Thyroid J*. 2012;1(2):55-71.
 28. Okosieme O, Gilbert J, Abraham P, Boelaert K, Dayan C, Gurnell M et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol*. 2015;84(6):799-808.
 29. Ladenson PW. Precision Medicine Comes to Thyroidology. *J Clin Endocrinol Metab*. 2016;101(3):799-803.
 30. World Health organisation. Pharmacovigilance [Internet]. 2019 [cited 2019 Sept 19]. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/.
 31. Radecka A, Loughlin L, Foy M, de Ferraz Guimaraes MV, Sarinic MV, Di Giusti MD et al. Enhancing Pharmacovigilance Capabilities in the EU Regulatory Network: The SCOPE Joint Action. *Drug Saf*. 2018;41(12):1285-302.
 32. Santoro A, Genov G, Spooner A, Raine J, Arlett P. Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works. *Drug Saf*. 2017;40(10):855–69.
 33. Coleman JJ, Pontefract SK. Adverse drug reactions. *Clin Med (Lond)*. 2016;16(5):481–5.
 34. Sferrazza G, Nicotera G, Pierimarchi P. Suspected adverse drug reactions (ADRs) trends in older Italian patients: an analysis from the National Pharmacovigilance Network. *Aging Clin Exp Res*. 2019. doi: 10.1007/s40520-019-01304-5.
 35. van Eekeren R, Rolfes L, Koster AS, Magro L, Parthasarathi G, Al Ramimmy et al. What Future Healthcare Professionals Need to Know About Pharmacovigilance: Introduction of the WHO PV Core Curriculum for University Teaching with Focus on Clinical Aspects. *Drug Saf*. 2018;41(11):1003-11.

36. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. *Drug Saf.* 2015;38(5):437–53.
37. Trifirò G, Gini R, Barone-Adesi F, Beghi F, Cantarutti A, Capuano A et al. The Role of European Healthcare Databases for Post-Marketing Drug Effectiveness, Safety and Value Evaluation: Where Does Italy Stand? *Drug Saf.* 2019;42(3):347–63.
38. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *Br J Clin Pharmacol.* 2004;57(2):121–6.
39. Varallo FR, Guimarães SdO, Abjaude SA, Mastroianni Pde C. Causes for the underreporting of adverse drug events by health professionals: a systematic review. *Rev esc enferm USP.* 2014;48(4):739-47.
40. Hohl CM, Small SS, Peddie D, Badke K, Bailey C, Balka E. Why Clinicians Don't Report Adverse Drug Events: Qualitative Study. *JMIR Public Health Surveill.* 2018;4(1):e21.
41. Marimuthu SP, Iyer G, Segal JB, Singh S. Patient-relevant outcomes associated with generic tamsulosin, levothyroxine and amphetamine in the FDA Adverse Event Reporting System: a pilot study. *J Comp Eff Res.* 2017;6(5):437-47.
42. Jonklaas J. Risks and safety of combination therapy for hypothyroidism. *Expert Rev Clin Pharmacol.* 2016;9(8):1057-67.
43. Scavone C, Sportiello L, Cimmaruta D, Sullo MG, Vitelli B, Rafaniello C et al. Medication adherence and the use of new pharmaceutical formulations: the case of levothyroxine. *Minerva Endocrinol.* 2016;41(2):279-89.

8. SUMMARY

Objectives: Hypothyroidism is a very common disorder and refers to all pathological conditions defined by deficiency of hormones thyroxine and triiodothyronine. The total prevalence, according to previously conducted studies, is around 3%, and of undiagnosed hypothyroidism it is 5%. Gold standard in treatment of this disease is levothyroxine.

Patients and Methods: Levothyroxine oral tablets marketed in Croatia were studied. Adverse drug reaction reports for levothyroxine obtained from 1 January 2006 to 31 December 2018 were included. The following data were analyzed: year, reporter qualification, patient gender and age, seriousness, concomitant therapy and system organic class according to MedDRA.

Results: During the period from 2006 to 2018, the total number of levothyroxine adverse drug reaction reports was 146. In the year 2018, 22.76% of all reports were obtained. Female gender reported adverse drug reactions predominantly; compared to male, 121 vs. 22 reports. In 75.2% of reports the only involved drug was levothyroxine. Pharmacists most commonly reported adverse drug reactions with 64 reports. Almost 75% of the reports were not classified as serious. Injury, poisoning and procedural complications, General disorders and administration site disorders and Gastrointestinal disorders with 16.9%, 15.3% and 11.2% of the reactions respectively were most commonly reported system organ classes.

Conclusion: During the examined period, reports of adverse drug reactions for oral tablets of levothyroxine were classified as not serious. Future studies should involve other countries reports and other drug formulations of levothyroxine in order to improve knowledge of levothyroxine safety profile.

9. CROATIAN SUMMARY

Naslov: Analiza spontano prijavljenih sumnji na nuspojave levotiroksina u Republici Hrvatskoj

Ciljevi: Hipotireoza je vrlo čest poremećaj, a odnosi se na sva patološka stanja definirana nedostatkom hormona tiroksina i trijodtironina. Prema prethodno provedenim istraživanjima ukupna učestalost u populaciji iznosi oko 3%, a nedijagnosticirane hipotireoze prema procjenama ima oko 5%. Zlatni standard u liječenju ove bolesti je levotiroksin.

Pacijenti i metode: U ovo istraživanje su uključene isključivo tablete za oralnu primjenu levotiroksina koje se nalaze na tržištu u Republici Hrvatskoj. Uključene su sumnje na nuspojave levotiroksina zaprimljene od 1. siječnja 2006. do 31. prosinca 2018. godine. Analizirani su sljedeći podaci: godina prijave, kvalifikacija izvjestitelja, spol i dob pacijenta, ozbiljnost nuspojave, istodobna primjena drugih lijekova u terapiji i organski sustavi prema MedDRA klasifikaciji.

Rezultati: Tijekom razdoblja od 2006. do 2018. godine ukupan broj sumnji na levotiroksin bio je 146. U 2018. godini prijavljeno je 22,76% svih sumnji. Ženski spol pretežno je izvjestio o nuspojavama lijekova, u usporedbi s muškim, 121 prema 22 prijave. U 75,2% prijava jedini lijek bio je levotiroksin. Ljekarnici su najčešće prijavljivali, s 64 prijavljene sumnje na nuspojave levotiroksina. Gotovo 75% sumnji nije klasificirano kao ozbiljno. Ozljede, trovanja i proceduralne komplikacije, Opći poremećaji i poremećaji na mjestu primjene te Gastrointestinalni poremećaji sa 16,9%, 15,3% i 11,2% reakcija najčešće su prijavljeni u sistemskim klasama sustava.

Zaključak: Tijekom ispitivanog razdoblja sumnje na nuspojave lijekova za levotiroksin nisu klasificirane kao ozbiljne. Buduća istraživanja trebaju uključivati podatke drugih zemalja, a i druge formulacije lijekova levotiroksina, kako bi se poboljšalo znanje o sigurnosnom profilu levotiroksina.

10. CURRICULUM VITAE

Personal information

Name: Ellen Sophie Koppmann

Date and place of birth: 30.04.1993 in Gütersloh, Germany

Nationality: German

E-mail: e.s.koppmann@t-online.de

Education

October 2013 – September 2019: Medical Studies in English, University of Split School of Medicine, Croatia

October 2012 – March 2013: Studies to become a teacher, Universität Bielefeld, Germany

August 2003 – June 2012: Ceciliengymnasium Bielefeld, Germany

September 2009 - November 2009: Kildonan East Collegiate, Winnipeg, Canada

Internships

February 2019: Internship in General and Visceral Surgery, Klinikum Bielefeld, Germany

January 2019: Internship in Internal Medicine, Klinikum Bielefeld, Germany

April 2013 - July 2013: Internship in Nursing, Krankenhaus Mara, Evangelisches Klinikum Bethel, Bielefeld, Germany

Languages

German (native language)

English (C1)

French (B2)

Croatian (A2)

Latin (Latinum)