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Review Article

A Review on Thyroxine Sodium: Pharmacovigilance, Potential Indications, Interactions, Precautions

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ABSTRACT

ADRs. A growing trend in pharmacovigilance is to connect premarketing data with human safety information observed during the post-marketing phase. Pharmacovigilance is crucial in healthcare, focusing on assessing, monitoring, and identifying interactions between drugs and their effects on humans. While pharmaceutical and biotechnological medications aim to cure, prevent, or treat diseases, they also carry risks, such as adverse drug reactions (ADRs), which can harm patients. Therefore, monitoring ADRs is essential for medication safety throughout its lifecycle, including during drug development, such as in the early stages of drug design, clinical trials, and post-marketing surveillance. Pharmacovigilance involves detecting, assessing, understanding, and preventing.

INTRODUCTION

Pharmacovigilance is a vital component of clinical research, encompassing both the safety of clinical trials and post-marketing surveillance throughout a product's lifecycle. It is defined as the scientific study concerned with detecting, assessing, understanding, and preventing adverse effects, particularly the short and long-term effects of medications. The official introduction of pharmacovigilance dates back to December 1961 when Dr. W. McBride, an Australian physician, published a letter (case report) in The Lancet. In this report, he was the first to suspect a link between the use of thalidomide during pregnancy and serious fetal deformities (phocomelia).

Oral levothyroxine (LT4) replacement therapy is the established treatment for hypothyroidism patients. Treatment aims to alleviate symptoms and normalize thyroid-stimulating hormone (TSH) levels in the blood. LT4 is available orally in various forms, including tablets, soft gel capsules, and liquid formulations. LT4 tablets are offered in both branded and generic versions. The conventional tablet form contains LT4 sodium, a stable salt, along with various inactive ingredients.

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The composition of these ingredients can influence tablet stability and pharmacokinetics.

Thyroxine sodium is classified under 'thyroid agents' and is primarily used to treat hypothyroidism, a condition where the thyroid gland, located in the front lower part of the neck, is unable to produce enough thyroid hormone. This hormone, composed of tri-iodothyronine (T3) and thyroxine (T4), regulates the body's energy usage. The thyroid gland also influences the functioning of the heart and digestive system. Without the correct levels of these hormones, the body cannot function properly. Early symptoms of hypothyroidism include fatigue and weight gain, while other symptoms may include feeling excessively cold, dry skin, irregular menstrual cycles (in women), easy fatigue, constipation, weight gain, or lack of energy. It is crucial to diagnose and treat hypothyroidism promptly to restore normal physical and mental function.

- **Potential indications and dosage:**

Levothyroxine Sodium Tablets are prescribed for replacement therapy in congenital or acquired hypothyroidism, whether it's primary (thyroidal), secondary (pituitary), or tertiary (hypothalamic). They are also used as an adjunct to surgery and radioiodine therapy in managing well-differentiated thyroid cancer that depends on thyrotropin for growth.

Nevertheless, it's essential to consider the following constraints:

- These tablets should not be used to suppress benign thyroid nodules and nontoxic diffuse goiter in patients with sufficient iodine levels. Doing so does not offer clinical benefits and may lead to hyperthyroidism.
- Levothyroxine Sodium Tablets should not be used to treat hypothyroidism during the recovery phase of subacute thyroiditis.

1 –IV Myxoedema coma

For the treatment of myxedema coma, the dosage of intravenous levothyroxine should be tailored to the patient's physical condition, age, cardiac risk factors, and the severity and duration of myxedema symptoms. An initial loading dose of 300-500 mcg is administered, followed by a maintenance dose of 50-100 mcg daily via intravenous injection. The dosage should not exceed a maximum rate of 100 mcg per minute.

For elderly patients, lower initial doses are recommended.

2-Oral TSH suppression

For adults, as an adjunct to surgery and radioiodine therapy for managing well-differentiated thyroid cancer dependent on thyrotropin, the dosage should be tailored to each patient. This should consider their clinical response, laboratory results, age, weight, cardiovascular status, concurrent conditions or medications, and the specific nature of the disease being treated. Doses exceeding 2 mcg/kg per day may be administered as a single dose to lower TSH levels to below 0.1 milliunits/L. For patients with high-risk tumors, the target TSH suppression level may be even lower. It's important to note that dosage and treatment recommendations may vary between different products or countries, so detailed product guidelines should be consulted.

3-Oral Hypothyroidism

Adults:

For replacement therapy in congenital or acquired cases, the dosage should be tailored to each patient based on their clinical response, laboratory results, age, weight, cardiovascular status, concurrent conditions or medications, and the specific nature of the disease being treated.

Initially, a daily dose of 50-100 mcg is recommended, which may be increased by 25-50 mcg every 3 to 4 weeks until the thyroid deficiency is corrected and a maintenance dose is established. The usual maintenance dose is 100-200 mcg daily.

Alternatively, the therapy can be initiated at approximately 1.6 mcg/kg daily, with adjustments made by 12.5-25 mcg increments every 4-6 weeks until serum TSH returns to normal and a euthyroid state is achieved. For patients over 50 years old, the initial dose is typically 12.5-50 mcg daily, which may be increased by 12.5-25 mcg increments at intervals ranging from approximately 2-8 weeks. The usual maintenance dose is 50-200 mcg daily. Dosage and treatment recommendations may vary among different products or countries, so detailed product guidelines should be consulted.

Elderly:

For elderly patients, the initial dose is usually 12.5-50 mcg daily as a single dose, which may be gradually increased by 12.5-25 mcg increments at intervals ranging from approximately 2-8 weeks. The usual maintenance dose is 50-200 mcg daily. Dosage and treatment recommendations may vary among different products or countries, so detailed product guidelines should be consulted.

Children:

For replacement therapy in congenital or acquired cases, the dosage should be individualized based on the child's age, clinical response, laboratory results, and the specific nature of the disease being treated. Neonates and infants: Initially, 10-15 mcg/kg daily for the first 3 months, then adjust the dose according to clinical findings, thyroid hormone, and TSH values. Children aged over 3 months: Initially, 12.5-50 mcg daily, with gradual increases every 2-4 weeks based on clinical findings, thyroid hormone, and TSH values until the full replacement dose is achieved. The usual maintenance dose is 100-150 mcg/m2 daily. Dosage and treatment recommendations may vary among different products or countries, so detailed product guidelines should be consulted.

4-Oral hypothyroidism

For adults, the dosage should be customized based on the patient's clinical response, laboratory results, age, weight, cardiovascular status, concurrent conditions or medications, and the specific nature of the disease being treated.

Initially, a daily dose of 12.5-25 mcg is recommended as a single dose. This dose may be gradually increased by increments of 12.5-25 mcg at 2- to 4-week intervals until serum TSH levels return to normal and a euthyroid state is achieved. It's important to note that dosage and treatment recommendations may vary among different products or countries, so detailed product guidelines should be consulted.

5. Special patients groups

Oral:

Hypothyroidism:

Patients with cardiovascular disease: Start with 12.5-50 mcg daily, with possible increases of 12.5-25 mcg every 2-8 weeks. The typical maintenance dose is 50-200 mcg daily. Specific dosage and treatment guidelines may differ between products or countries (consult detailed product guidelines). Neonates (0-3 months) at risk of cardiac failure: Consider starting with lower initial doses. Adjust the dose every 4-6 weeks based on clinical and laboratory response, as needed. Older children at risk of hyperactivity: Begin with 1/4 of the recommended full replacement dose. Increase the dose by 1/4 of the full recommended replacement dose weekly until the full replacement dose is reached.

Intravenous:

Patients with underlying cardiovascular disease: Start with lower doses.

- **Adverse reactions:**

Most adverse reactions related to Levothyroxine Sodium Tablets therapy stem from therapeutic overdosage and manifest as symptoms of hyperthyroidism.

They include the following

- General: Symptoms may include fatigue, heightened appetite, weight loss, intolerance to heat, fever, and excessive sweating.
- Central nervous system: headache, hyperactivity, nervousness, anxiety, irritability, emotional changes, insomnia
- Musculoskeletal: tremors, muscle weakness, muscle spasms
- Cardiovascular: palpitations, rapid heartbeat, irregular heart rhythms, increased pulse and blood pressure, heart failure, chest pain, heart attack, cardiac arrest
- Respiratory: difficulty breathing
- Gastrointestinal: diarrhea, vomiting, abdominal cramps, elevated liver function tests
- Dermatologic: hair loss, flushing, rash
- Endocrine: decreased bone mineral density
- Reproductive: irregular menstrual cycles, decreased fertility
- Rarely, seizures have been reported following the initiation of levothyroxine therapy.

Adverse Reactions in Children:

Children receiving levothyroxine therapy have been reported to experience pseudotumor cerebri and slipped capital femoral epiphysis. Excessive treatment may lead to craniosynostosis in infants and premature closure of the epiphyses in children, which could affect their adult height.

Hypersensitivity Reactions:

Patients treated with thyroid hormone products have experienced hypersensitivity reactions to inactive ingredients. These reactions include urticaria, itching, skin rash, flushing, swelling, various gastrointestinal symptoms (such as abdominal pain, nausea, vomiting, and diarrhea), fever, joint pain, serum sickness, and wheezing. It is not known for patients to have hypersensitivity to levothyroxine itself.

- **Drug interactions:**

Drug –drug interactions

Carbamazepine, phenytoin, phenobarbital, primidone, and rifampicin can enhance or increase the metabolism of levothyroxine. The absorption of levothyroxine may be reduced when taken with antacids, cimetidine, proton pump inhibitors (PPIs), sucralfate, oral iron, calcium salts, phosphate binders (such as sevelamer), bile acid sequestrants (such as cholestyramine, colestipol), ion exchange resins (such as sodium polystyrene sulfonate), and orlistat. There is a risk of marked tachycardia and hypertension when levothyroxine is taken with ketamine. The effects of digitalis glycosides may be decreased. There is an increased risk of cardiac arrhythmias and central nervous system stimulation when levothyroxine is taken with tricyclic antidepressants (such as amitriptyline). When taken with anti-inflammatory agents (such as aspirin, phenylbutazone), levothyroxine may result in falsely low plasma concentrations. The effects of anticoagulants (such as warfarin) and sympathomimetic agents (such as phenylephrine, epinephrine) may be increased. Sertraline, tyrosine kinase inhibitors (such as imatinib), and estrogen derivatives may reduce the effects of levothyroxine sodium. Androgens and corticosteroids may decrease serum levels of levothyroxine-binding globulins. The peripheral conversion of levothyroxine sodium to triiodothyronine may be inhibited by amiodarone and β-blockers (such as propranolol), resulting in reduced efficacy. Levothyroxine may increase the dose requirements of antidiabetic drugs.

Drug- food interactions

Co-administration with enteral nutrition can lead to decreased bioavailability and serum levels of thyroxine. Absorption may be reduced when taken with certain foods like soybean flour, cottonseed meal, walnuts, and dietary fiber. Grapefruit juice may delay absorption and reduce bioavailability.

Precaution:

1-Elderly patients and those with underlying cardiovascular disease: They may experience cardiac adverse reactions due to overtreatment with levothyroxine. This may include an increase in heart rate, cardiac wall thickness, and cardiac contractility, potentially leading to angina or arrhythmias. Therefore, it is advisable to initiate Levothyroxine Sodium Tablets therapy at lower doses in this population compared to younger individuals or those without cardiac disease. Patients with coronary artery disease receiving suppressive Levothyroxine Sodium Tablets therapy should be monitored for cardiac arrhythmias during surgical procedures. Patients receiving concomitant Levothyroxine Sodium Tablets and sympathomimetic agents should be monitored for signs and symptoms of coronary insufficiency. If cardiac symptoms develop or worsen, the dose of Levothyroxine Sodium Tablets should be reduced or withheld for one week before restarting at a lower dose.

2-Myxedema Coma:

Myxedema coma is a life-threatening emergency characterized by poor circulation and reduced metabolism. In such cases, the absorption of levothyroxine sodium from the gastrointestinal tract can be unpredictable. Therefore, the use of oral thyroid hormone medications is not recommended for treating myxedema coma. Instead, thyroid hormone products formulated for intravenous administration should be used to manage myxedema coma.

3-Acute Adrenal Crisis in Patients with Concomitant Adrenal Insufficiency:

Thyroid hormone increases the metabolic clearance of glucocorticoids. Starting thyroid hormone therapy before initiating glucocorticoid therapy may trigger an acute adrenal crisis in patients with adrenal insufficiency. Therefore, it is recommended to administer replacement glucocorticoids to patients with adrenal insufficiency before starting treatment with Levothyroxine Sodium Tablets.

4-Worsening of Diabetic Control:

Adding levothyroxine therapy to patients with diabetes mellitus may exacerbate glycemic control issues and lead to an increase in the requirements for antidiabetic agents or insulin. It is important to closely monitor glycemic control when initiating, adjusting, or discontinuing Levothyroxine Sodium Tablets.

5-Decreased Bone Mineral Density Associated with Thyroid Hormone Over-Replacement:

Over-replacement of levothyroxine, especially in post-menopausal women, may lead to increased bone resorption and decreased bone mineral density. This increased bone resorption may result in higher serum levels and urinary excretion of calcium and phosphorous, elevated bone alkaline phosphatase levels, and suppressed serum parathyroid hormone levels. To reduce this risk, administer the lowest effective dose of Levothyroxine Sodium Tablets necessary to achieve the desired clinical and biochemical response.

CONCLUSION:

Levothyroxine is prescribed to treat hypothyroidism, a condition characterized by an underactive thyroid gland. It works by replacing or supplementing the thyroid hormone that is normally produced by the thyroid gland. Hypothyroidism can occur naturally or as a result of thyroid gland injury due to radiation, medications, or surgical removal.

It's important to note that thyroid hormones, including levothyroxine, should not be used alone or with other medications for the purpose of treating obesity or facilitating weight loss. In individuals with normal thyroid function, doses of levothyroxine that fall within the range of daily hormonal requirements are ineffective for weight reduction. Additionally, larger doses can lead to

serious or life-threatening symptoms of toxicity, especially when taken with sympathomimetic amines used for their appetite-suppressant effects.

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