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A REVIEW ON THYROXINE SODIUM: PHARMACOVIGILANCE, POTENTIAL INDICATIONS, INTERACTIONS, PRECAUTIONS

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ABSTRACT

Pharmacovigilance plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human. Pharmaceutical and biotechnological medicines are designed to cure, prevent or treat diseases; however, there are also risks particularly adverse drug reactions (ADRs) can cause serious harm to patients. Thus, for safety medication ADRs monitoring is required for each medicine throughout its life cycle, during development of drug such as pre-marketing including early stages of drug design, clinical trials, and post-marketing surveillance. PV is concerned with the detection, assessment, understanding and prevention of ADRs. The emerging trend in PV is to link premarketing data with human safety information observed in the post-marketing phase.

KEYWORDS: Pharmacovigilance, hypothyroidism, indications, interactions, levothyroxine.

INTRODUCTION

Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product lifecycle. Pharmacovigilance is "defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short-term adverse effects of medicines." Pharmacovigilance (PV) was officially introduced in December 1961 with the publication of a letter (case report) in the Lancet by W. McBride, the Australian doctor who first suspected a causal link between serious fetal deformities (phocomelia) and thalidomide, a drug used during pregnancy[1].

Thyroid hormone replacement therapy with oral levothyroxine (LT4) is the standard treatment for patients with hypothyroidism[2]. The goals of treatment include resolution of

symptoms and signs of hypothyroidism and normalization of circulating thyroid-stimulating hormone (TSH) levels. Orally administered LT4 is available in several formulations (including tablet, soft gel capsule and liquid formulations), and LT4 tablets are available in multiple branded and generic forms[3]. The traditional tablet formulation contains LT4 sodium, a stable salt, and a variety of inactive excipients, the composition of which may affect tablet stability and pharmacokinetics[4].

Thyroxine Sodium belongs to 'thyroid agents', primarily used to treat underactive thyroid (hypothyroidism). Hypothyroidism is a chronic disorder, which happens when the thyroid gland (located in the front lower part of the neck), is unable to make enough thyroid hormone. The thyroid gland is responsible for releasing hormones, which are composed of tri-iodothyronine (T3) and thyroxine (T4), which helps the body to regulate and use energy. The thyroid controls functions of the heart and digestive system, without the right amount of these hormones, the body is unable to function properly. Early symptoms of this disease are fatigue and weight gain[5]. While other symptoms include feeling cold even in warm weather, dry skin or too much or too few menses (in women), easy fatigueness, constipation, weight gain, or even lack of energy. The right diagnosis and treatment of hypothyroid are important to restore normal physical and mental activity[6].

- **Potential indications and dosage**

Hypothyroidism Levothyroxine Sodium Tablets are indicated as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.

Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression Levothyroxine Sodium Tablets are indicated as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer[7].

Limitations of Use

- Levothyroxine Sodium Tablets are not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients as there are no clinical benefits and overtreatment with Levothyroxine Sodium Tablets may induce hyperthyroidism.
- Levothyroxine Sodium Tablets are not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis[8].

1 -Intravenous

Myxoedema coma

Adult: Individualize dosage based on patient's physical condition, age, cardiac risk factors, and clinical severity and duration of myxoedema symptoms. Initially, 300-500 mcg as loading dose, followed by a maintenance dose of 50-100 mcg daily until the patient is stable and can tolerate oral treatment. Doses are given via IV inj at a Max rate of 100 mcg/min. **Elderly**: Initiate at lower doses[9].

2-Oral TSH suppression

Adult: Adjunct to surgery and radioiodine therapy to manage thyrotropin-dependent well-differentiated thyroid cancer: Individualise dosage based on patient's clinical response, laboratory parameters, age, weight, CV status, concurrent conditions or medications, and nature of disease being treated. Doses >2 mcg/kg daily may be given as a single dose to suppress TSH levels to <0.1 milliunits/L. In patients with high-risk tumors, the target level for TSH suppression may be lower. Dosage and treatment recommendations may vary among individual products or countries (refer to detailed product guidelines)[10].

3-Oral Hypothyroidism

Adult: Replacement therapy in congenital or acquired cases: Individualise dosage based on patient's clinical response, laboratory parameters, age, weight, CV status, concurrent conditions or medications, and nature of disease being treated. Initially, 50-100 mcg daily, may increase by 25-50 mcg at approx. 3- to 4-week intervals until thyroid deficiency is corrected and maintenance dose is established. Usual maintenance: 100-200 mcg daily. Alternatively, initiate at approx. 1.6 mcg/kg daily, adjusted by 12.5-25 mcg increments every 4-6 weeks until serum TSH returns to normal and euthyroid state is achieved. *>50 years* Initially, 12.5-50 mcg daily, may be increased by 12.5-25 mcg increments at intervals ranging from approx. 2-8 weeks. Usual maintenance: 50-200 mcg daily. Daily doses are taken as a single dose. Dosage and treatment recommendations may vary among individual products or countries (refer to detailed product guidelines).

Elderly: Initially, 12.5-50 mcg daily as a single dose, may be increased gradually by 12.5-25 mcg increments at intervals ranging from approx. 2-8 weeks. Usual maintenance: 50-200 mcg daily. Dosage and treatment recommendations may vary among individual products or countries (refer to detailed product guidelines).

Child: Replacement therapy in congenital or acquired cases: *0-3 months* 10-15 mcg/kg daily; *>3-6 months* 8-10 mcg/kg daily; *>6-12 months* 6-8 mcg/kg daily; *1-5 years* 5-6 mcg/kg daily; *6-12 years* 4-5 mcg/kg daily. *>12 years* Patients with incomplete growth and puberty: 2-3 mcg/kg daily; Patients with complete growth and puberty: Approx 1.6 mcg/kg daily, adjusted by 12.5-25 mcg increments every 4-6 weeks until serum TSH returns to normal and euthyroid state is achieved. Individually adjust dose based on response and laboratory parameters. Alternative dosing regimens: For congenital cases: *Neonates and infants* Initially, 10-15 mcg/kg daily for the 1st 3 months, then individually adjust dose according to clinical findings, thyroid hormone and TSH values. For acquired cases: *Children* Initially, 12.5-50 mcg daily, then increase gradually every 2-4 weeks based on clinical findings, thyroid hormone and TSH values until full replacement dose is achieved. Maintenance: 100-150 mcg/m^2 daily. Daily doses are given as a single dose. Dosage and treatment recommendations may vary among individual products or countries (refer to detailed product guidelines)[11].

4-Oral

Severe and chronic hypothyroidism

Adult: Individualise dosage based on patient's clinical response, laboratory parameters, age, weight, CV status, concurrent conditions or medications, and nature of disease being treated. Initially, 12.5-25 mcg daily as a single dose, may be increased gradually by increments of 12.5-25 mcg at 2- to 4-week intervals until serum TSH levels return to normal and euthyroid state is achieved. Dosage and treatment recommendations may vary among individual products or countries (refer to detailed product guidelines)[12].

5-Special Patient Group

Oral: Hypothyroidism

Patients with CV disease: Initially, 12.5-50 mcg daily, may be increased by 12.5-25 mcg increments at intervals of approx. 2-8 weeks. Usual maintenance: 50-200 mcg daily. Dosage and treatment recommendations may vary among individual products or countries (refer to detailed product guidelines)[13].

Neonates (0-3 months) **at risk of cardiac failure**: Lower initial doses may be considered. Increase dose at 4- to 6-week intervals depending on clinical and laboratory response, as necessary.

Older children at risk of hyperactivity: Initiate at 1/4 of the recommended full replacement dose. Increase dose by 1/4 of the full recommended replacement dose at weekly intervals until full replacement dose is achieved.

IV:

Patient with underlying CV disease: Initiate at lower doses.

Adverse reactions

Adverse reactions associated with Levothyroxine Sodium Tablets therapy are primarily those of hyperthyroidism due to therapeutic overdosage.

They include the following

- General: fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating
- Central nervous system: headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia
- Musculoskeletal: tremors, muscle weakness, muscle spasm
- Cardiovascular: palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest
- Respiratory: dyspnea
- Gastrointestinal: diarrhea, vomiting, abdominal cramps, elevations in liver function tests
- Dermatologic: hair loss, flushing, rash
- Endocrine: decreased bone mineral density
- Reproductive: menstrual irregularities, impaired fertility Seizures have been reported rarely with the institution of levothyroxine therapy.

Adverse Reactions in Children

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Hypersensitivity Reactions

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema,

various gastrointestinal symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness, and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

- **Drug interactions**

Drug Interactions

Enhanced or increased metabolism with carbamazepine, phenytoin, phenobarbital, primidone, and rifampicin. May reduce absorption with antacids, cimetidine, PPIs, sucralfate, oral Fe, Ca salts, phosphate binders (e.g. sevelamer), bile acid sequestrants (e.g. cholestyramine, colestipol), ion exchange resins (e.g. sodium polystyrene sulfonate), and orlistat. Risk of marked tachycardia and hypertension with ketamine. May decrease the effects of digitalis glycosides. Increased risk of cardiac arrhythmias and CNS stimulation with TCAs (e.g. amitriptyline). May result in false low plasma concentration when given with anti-inflammatory agents (e.g. aspirin, phenylbutazone). May increase the effects of anticoagulants (e.g. warfarin) and sympathomimetic agents (e.g. phenylephrine, epinephrine). Sertraline, tyrosine kinase inhibitors (e.g. imatinib), and estrogen derivatives may reduce the effects of levothyroxine sodium. Androgens and corticosteroids may decrease the levothyroxine-binding globulins serum levels. Peripheral conversion of levothyroxine sodium to triiodothyronine may be inhibited by amiodarone and β-blockers (e.g. propranolol), resulting in reduced efficacy. May cause an increase in dose requirements of antidiabetic drugs.

Food Interaction

Concomitant administration with enteral nutrition may result in decreased bioavailability and serum thyroxine levels. May reduce absorption with certain foods (e.g. soybean flour, cottonseed meal, walnuts, dietary fiber). May delay absorption and reduce bioavailability with grapefruit juice.

Precaution

1- Cardiac Adverse Reactions in the Elderly and in Patients with Underlying Cardiovascular Disease: Over-treatment with levothyroxine may cause an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias, particularly in patients with cardiovascular disease and in elderly patients. Initiate Levothyroxine Sodium Tablets therapy in this population at lower doses than those recommended in younger individuals or in patients without cardiac disease [see Dosage and

Administration (2.3), Use in Specific Populations (8.5)]. Monitor for cardiac arrhythmias during surgical procedures in patients with coronary artery disease receiving suppressive Levothyroxine Sodium Tablets therapy. Monitor patients receiving concomitant Levothyroxine Sodium Tablets and sympathomimetic agents for signs and symptoms of coronary insufficiency. If cardiac symptoms develop or worsen, reduce the Levothyroxine Sodium Tablets dose or withhold for one week and restart at a lower dose.

2-Myxedema Coma

Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Use of oral thyroid hormone drug products is not recommended to treat myxedema coma. Administer thyroid hormone products formulated for intravenous administration to treat myxedema coma[14].

3-Acute Adrenal Crisis in Patients with Concomitant Adrenal Insufficiency

Thyroid hormone increases metabolic clearance of glucocorticoids. Initiation of thyroid hormone therapy prior to initiating glucocorticoid therapy may precipitate an acute adrenal crisis in patients with adrenal insufficiency. Treat patients with adrenal insufficiency with replacement glucocorticoids prior to initiating treatment with Levothyroxine Sodium Tablets.

4-Worsening of Diabetic Control

Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control after starting, changing, or discontinuing Levothyroxine Sodium Tablets.

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

Increased bone resorption and decreased bone mineral density may occur because of levothyroxine over-replacement, particularly in post-menopausal women. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase, and suppressed serum parathyroid hormone levels. Administer the minimum dose of Levothyroxine Sodium Tablets that achieves the desired clinical and biochemical response to mitigate this risk[15].

CONCLUSION

Levothyroxine is used to treat an underactive thyroid gland (hypothyroidism). It replaces or provides more thyroid hormone, which is normally produced by the thyroid gland. Low thyroid hormone levels can occur naturally or when the thyroid gland is injured by radiation/medications or removed by surgery. Thyroid hormones, including levothyroxine, should not be used either alone or with other therapeutic agents for the treatment of obesity or weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

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