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Liothyronine: A drug of choice for Hypothyroidism

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ABSTRACT: Hypothyroidism is one of the most common endocrine disorder in which there is insufficient production of thyroid hormone. The disorder affects nearly 10% of the world population. Thyroid hormone drugs namely tetraiodothyronine (T4, levothyroxine sodium) or triiodothyronine (T3, liothyronine sodium) are used to treat thyroid deficiency. In some patients treated with levothyroxine (T4) still develop residual symptoms of hypothyroidism. In such patients liothyronine is the drug of choice. This review article provides an exhaustive account in illustrating the pharmacology, applications, adverse effects, precautions, interaction, posology and overdosage of the drug liothyronine.

KEYWORDS: Thyroid hormone, levothyroxine sodium, liothyronine sodium, Hypothyroidism

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I. INTRODUCTION:

[1]. The thyroid is a small butterfly shaped gland that lies just under the skin below the adams apple in the neck and measures about 2 inches transversely. The normal thyroid gland secretes two important hormones tetraiodothyronine (T4) and triiodothyronine (T3) due to stimulation of TSH hormone of anterior pituitary gland. These hormones regulate various metabolic process of body like lipid, carbohydrates, protein metabolism, etc. [2].These hormones also influence linear growth, brain function including intelligence and memory, neural development, dentition and bone development. These hormones are synthesised in the thyroid gland with the help of proteins and iodine supplied by the diet.

Hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormone. It is sometimes referred to as an underactive thyroid. When the condition is severe it is called myxoedema (non pittingedema). There are two types of hypothyroidism- primary hypothyroidism and secondary hypothyroidism. The most common cause of primary hypothyroidism is acquired by the result of destruction of the gland by an auto immune disease (Hashimoto's thyroiditis) or by radioactive iodine therapy or surgery for hyperthyroidism. About 95% of the time hypothyroidism is the result of malfunction of thyroid gland itself (primary hypothyroidism).

Secondary hypothyroidism is a result of problem outside the thyroid gland. Tumors or other abnormalities of the hypothalamus or pituitary gland are examples of condition that can cause secondary hypothyroidism. Some drugs can also cause hypothyroidism (eg: lithium carbonate, para amino salicylic acid, thio urea drugs, sulphonamides, phenylbutazone and others. Decades ago congenital hypothyroidism was a common cause of mental retardation and severe disability in affected children.

EPIDEMOLOGY:

[3]. The prevalence of hypothyroidism in developed countries is about 4% - 5%, whereas in India it is reported to be around 10.95%. as per the epidemiology study conducted by Unnikrishnan etal. In eight cities of India, the prevalence of subclinical hypothyroidism (SCH), a mild thyroid failure, was found to be 8.02%. [3,4]. The prevalence of SCH ranges between 4% and 15% worldwide and is reported to be 11.4% for women and 6.2% for men in India. [5]. Among the Indian population, patients with asthma, obesity, diabetes, dyslipidemia and hypertension had the higher prevalence of hypothyroidism. The prevalence of hypothyroidism in pregnancy with TSH was found to be 13.13%.

The ideal therapeutic goal of hypothyroidism is to restore clinical and biochemical euthyroidism via physiologic thyroid hormone replacement therapy. For the past decades, the standard treatment for thyroid hormone deficiency is thyroid hormone replacement is by administrating levothyroxine (T4) at doses that

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normalise the serum TSH. There are certain drawbacks in T4 replacement therapy. Evidence suggests a significant proportion of patient treated with T4 still have the residual symptoms of hypothyroidism. The one basic reason behind is that the serum level of active T3 might not be fully normalised (T4 to T3 conversion). Similar results were also reported by clinical studies and animal studies. To overcome the drawbacks liothyronine (T3) is preferred over levothyroxine (T4) in the treatment of hypothyroidism. So in this review article dicusses in detail about the drug Liothyronine

II. PHARMACOLOGY

Indication

[6]. Liothyronine is officially approved for the following indications:

- Replacement therapy in primary (thyroidal), secondary (pituitary) and tertiary (hypothalamic) congenital or acquired hypothyroidism.
- As an adjunct therapy to surgery and radio iodine in the management of thyroid cancer.
- As a diagnostic agent in suppression tests for mild hyperthyroidism or thyroid gland autonomy

In general terms, exogenous liothyronine is used to replace insufficient hormonal production and restore T3 plasma levels. The lack of liothyronine can be presented as a pale and puffy face, coarse, brittle hair, dry skin, croaky voice and constipation as well as irregular periods, drowsiness, and lethargy. Liothyronine should never be used in the suppression of benign nodules and nontoxic diffuse goitre in iodine-sufficient patients nor in the treatment of hyperthyroidism during the recovery phase of subacute thyroiditis.

Pharmacodynamics

[7]. In hormonal replacement, liothyronine is more potent and present a faster action when compared to levothyroxine but the time of action is significantly shorter. The onset of activity is observed in a few hours after administration and the maximum effect is observed after 2-3 days. Treatment with liothyronine has been shown to produce normal plasma levels of T3 hormone but to have no effect on the T4 plasma concentration.

Mechanism of action

[8]. Liothyronine replaces endogenous thyroid hormone and then exerts its physiologic effects by controlling DNA transcription and protein synthesis. This effect on DNA is obtained by the binding of liothyronine to the thyroid receptors attached to DNA. Exogenous liothyronine exerts all the normal effects of the endogenous thyroid T3 hormone. Hence, it increases energy expenditure, accelerates the rate of cellular oxidation stimulating growth, maturation, and metabolism of the body tissues, aids in myelination of nerves and development of synaptic processes in the nervous system and enhances carbohydrate and protein metabolism.

Absorption

[9]. Thyroid hormones are well absorbed orally. From these hormones, liothyronine is almost completely absorbed and it does not present changes in the absorption rate due to concomitant administration of food. Multiple administration of 50 mcg of liothyronine provided a maximal plasma concentration of total T3 of 346 ng/dL in about 2.5 hours with an AUC of 4740 ng.h/Dl.

Volume of distribution

[10]. The reported volume of distribution of liothyronine is reported to be of 0.1-0.2 L/kg

Proteinbinding

[11]. Liothyronine highly binds to plasma proteins and around 99.7% of the administered dose can be found bound. [12]. Liothyronine is found to be bound to thyroxine-binding globulin, thyroxine-binding prealbumin and albumin. It is important to consider that only the little unbound portion of liothyronine is metabolically active.

Metabolism

[12]. Liothyronine is mainly metabolized in the liver where it is de-iodinated to di-iodothyronine and mono-iodothyronine followed by conjugation with glucuronides and sulphates. [10]. One of the formed metabolites formed by the conjugation and decarboxylation is tiratricol. The iodine released by the metabolism of liothyronine is later taken and used within the thyroid cells

Route of elimination

[12]. The main elimination of thyroid hormones is known to be done via the kidneys from which less than 2.5% of the excreted drug is represented by the unchanged drug. This elimination route is reduced with age. A portion of the metabolic products of liothyronine is excreted to the bile and gut where they can be part of entero-hepatic recirculation

Half-life

[11]. The half-life of liothyronine is reported to be between 1 and 2 days

Toxicity

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[13]. The reported oral LD50 of liothyronine in the rat is higher than 4540 mg/kg. When overdosage is registered, symptoms of hyperthyroidism are reported as well as confusion, disorientation, cerebral embolism, seizure, shock, coma, and death. The symptoms of overdose can be presented immediately or several days after overdose ingestion. In an overdose state, reduce the dose of liothyronine and do supportive treatment

There are no reports studying the carcinogenic, and mutagenic potential nor on the effects of liothyronine on fertility

III. APPICATIONS:

- ✓ Hypothyroidism - Liothyronine is used to treat an underactive thyroid (hypothyroidism). It replaces or provides more thyroid hormone, which is normally made by the thyroid gland. Liothyronine is a man-made form of thyroid hormone.
- ✓ [14]. Thyroid carcinoma - Liothyronine reduces accumulated dose of thyroid and fastens excretion from the body after 48 h.
- ✓ [15]. Triiodothyronine (liothyronine sodium) may be used occasionally when a quicker onset of action is desired. Example: Preparing a patient for (131)I therapy for treatment of thyroid cancer.
- ✓ [15]. Myexedema coma - Liothyronine is also used for the treatmentof myexedema coma.
- ✓ [16]. Skin wounds in Diabetic Wistar Rats - Topical liothyronine is an effective, inexpensive and probably safe therapeutic option for diabetic ulcers in wistar rats
- ✓ [17]. Depression - T3 augmentation appears to be a safe and effective alternative treatment for euthyroid patients with uni-polar depression who receive appropriate baseline and follow-up safety monitoring.

IV. ADVERSE EFFECTS:

- ✓ [18]. Temporary hair loss may occur during the first few months of starting this drug, especially in children. Liothyronine therapy generally is well-tolerated. If symptoms occur, they usually occur because there are toxic (too high) levels of thyroid hormone (hyperthyroidism)
- ✓ Symptoms of hyperthyroidism includes, chest pain, increased heart rate, excessive sweating, heat tolerance, nervousness, headache, tremor, insomnia, diarrhoea, vomiting, weight loss, fever and rarely cardiac arrest.
- ✓ [19]. Liothyronine apart from therapeutic effects may cause some unwanted side effects such as anxiety, weight gain/loss, diarrhoea, difficulty in breathing, dizziness, sweating, extreme tiredness or weakness, fainting, irregular heart beat, feeling of discomfort, heat intolerance and impaired fertility.

V. PRECAUTIONS:

- ✓ [20]. Excessive dose should be avoided in cardiac patients.
- ✓ [21]. Liothyronine labelled with Iodine (125 or 131) is used for invitro evaluation of thyroid function. This preparation has high specific activity and causes radiation damage. So this dose is not for internal use.
- ✓ [21]. Use of liothyronine other than replacement therapy such as improvement of mood disorders, fatigue, lethargy, menstrual irregularities, etc.there are chances of untoward effects may be produced. Liothyronine does not improve such conditions.
- ✓ [22]. Use of liothyronine sodium in obese euthyroid individuals for weight loss should be avoided.
- ✓ [23]. The requirements of liothyronine sodium for thyroid hormone replacement patients above 60 years of age is 25% lower when compared to young adults. Therefore, the dose should be individualised.
- ✓ [24]. Thyroid function status should be periodically accessed for patients receiving liothyronine sodium since myxedema patients are very sensitive to thyroid agents, so with low doses the replacement therapy should be initiated and then the dose is increased gradually.
- ✓ [24]. Liothyronine sodium tablets should be stored in oxygen impervious air tight containers at a temperature less than 40 °C, preferably 15-30 °C. Liothyronine sodium injection should be stored at 2-8 °C.

VI. INTERACTIONS:

- ✓ [22]. Liothyronine in conjugation with propranolol decrease the risk of arrthythmia and angina is reported.
- ✓ [25]. Liothyronine produces hyper metabolic state due to increase in the decay of vitamin k-dependent clotting factors and in the presence of oral anti coagulants (eg. Warfarin), normal compensation by increase synthesis is prevented.
- ✓ [26]. Liothyronine prevent the lag time that occurs before clinical effectiveness of tricyclic anti depressants.

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- ✓ [27]. Liothyronine and cholestyramine are given simultaneously, cholestyramine decrease the absorption of liothyronine.
- ✓ [28]. The decrease of intraocular pressure by liothyronine in rabbits is blocked by systemic propranolol.
- ✓ [17]. Insulin inhibits liothyronine binding and hence development of hypothyroidism.
- ✓ [23]. Tricyclic anti depressants when used in combination with liothyronine sodium may increase the therapeutic and toxic effect of both the drugs. It is due to the catecholamines sensitivity to receptor is increased.
- ✓ [23]. Liothyronine may increase the requirement of insulin or antidiabetic agent during replacement therapy.
- ✓ [23]. Peripheral conversion of T4 (thyroxine) to T3 (triiodothyronine) is prevented when liothyronine is used with beta- adrenergic blocking agents.
- ✓ [23]. Cholestyramine and colestipol decrease the effects of liothyronine by binding, delaying, or preventing absorption. So 4 – 5 hours interval is necessary.
- ✓ [23]. Concurrent use of liothyronine with ketamine hydrochloride may produce marked hypertension and tachycardia.

Table 1. INTERACTION OF LIOTHYRONINE WITH OTHER DRUGS

DRUGS	INTERACTION
Acetaminophen	Liothyronine decreases the excretion rate of acetaminophen resultingin a higher serum level.
Amoxicillin	Liothyronine decreases the excretion rate of Amoxicillin resulting in a higher serum level.
Atenolol	The therapeutic efficacy of Liothyronine decreases when used with Atenolol combination.
Captopril	The excretion of Captopril is decreased when combined with Liothyronine.
Carbamazepine	Liothyronine decreases the excretion rate of Carbamazepine resulting in a higher serum level.
Diazepam	The therapeutic efficacy of Diazepam is decreased when it is used in combination withliothyronine
Digoxin	The serum concentration of Liothyronine is decreased when it is combined with Digoxin.
Dobutamine	The severity of adverse effects is increased when Liothyronine is combined with Dobutamine.
Dopamine	The severity of adverse effects is increased when Liothyronine is combined with Dopamine.
Ethambutol	Liothyronine decreases the excretion rate of Ethambutol resulting in a higher serum level.
Furosemide	The protein binding of Furosemide is decreased when combined with Liothyronine.
Gentamicin	Gentamicin decreases the excretion rate of Liothyronine resulting in a higher serum level.
Gliclazide	The therapeutic efficacy of Gliclazide is decreased when used in combination with Liothyronine.
Glipizide	The therapeutic efficacy of Glipizide is decreased when used in combination with Liothyronine.
Hydrocortisone	The excretion of Hydrocortisone is decreased when combined with Liothyronine.
Insulin human	The therapeutic efficacy of Insulin human is decreased when used in combination with Liothyronine.
Lithium carbonate	Liothyronine decreases the excretion rate of Lithium carbonate resulting in a higher

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	serum level.
Metformin	The therapeutic efficacy of Metformin is decreased when used in combination with Liothyronine.
Phenytoin	The metabolism of Liothyronine is increased when combined with Phenytoin.
Rifamycin	The excretion of Liothyronine is decreased when combined with Rifamycin.
Salbutamol	Liothyronine decreases the excretion rate of Salbutamol which could result in a higher serum level.

VII. POSOLOGY:

A. Padeiatric Dose For Hypothyroidism:
Congenital Hypothyroidism:

Initial dose: 5 mcg orally once a day, may be increased by upto 5 mcg/day increments every three to four days until desired response is achieved. Maintenance dose: Infants a few months old may require only 20 mcg per day. Patients at 1 year require 50 mcg per day. For patients above 3 years, the full adult dose may be necessary.

B. Geriatic Dose For Hypothyroidism:
Initiated at 5 mcg oral once a day and increased by not more than 5 mcg.

VIII. OVERDOSE:

Overdose of liothyronine sodium causes hyperthyroidism like side effects such as agitation, confusion, irritability, hyperactivity, headache, sweating, mydriasis, tachycardia, arrthythmias, tachypnoea, pyrexia, increased bowel movements and convulsions.

IX. CONCLUSION:

Recently many clinical and animal studies have reported that levothyroxine (T4) treatment for hypothyroidism does not fully normalise the serum active hormone T3 level. Hence significant proportion of patients treated with T4 still have the residual symptoms of hypothyroidism. To overcome this problem liothyronine T3 is used in the treatment to normalise the serum T3 level. Accordingly this review article presented a broad description about the drug liothyronine.

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