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Levothyroxine Use in Infants and Children with Congenital or Acquired Hypothyroidism

Marcia L. Buck, Pharm.D., FCCP

Replacement of endogenous L-thyroxine (T_4) with synthetic levothyroxine has had a significant impact on the long-term effects of both congenital and acquired hypothyroidism in pediatric patients.[1] While the use of levothyroxine in chronic hypothyroid states is well established, new research also suggests a potential benefit of thyroid replacement in the early management of autoimmune thyroiditis and in transient hypothyroid states such as prematurity. This issue of *Pediatric Pharmacotherapy* will provide an overview of the use of levothyroxine in infants and children with hypothyroidism, as well as a brief review of the drug's pharmacokinetics, drug interactions, adverse effects, and dosing recommendations.

Mechanism of Action

Release of T_4 is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and triggers secretion of thyrotropin-stimulating hormone (TSH) from the anterior pituitary. The presence of TSH stimulates synthesis and secretion of T_4 and L-triiodothyronine (T_3) by the thyroid. When serum concentrations of T_3 and T_4 increase, secretion of TRH and TSH declines.[2,3]

While the exact mechanisms of action for T_3 and T_4 are not well understood, they appear to work through control of DNA transcription and protein synthesis. Both T_3 and T_4 have the ability to diffuse into the cell nucleus and bind to thyroid hormone receptor proteins on DNA. This binding results in their ability to regulate a variety of metabolic processes influencing normal growth and development, maturation of the central nervous system, and bone formation. Although both T_3 and T_4 are active, T_3 is the predominate form throughout the body. The majority of circulating T_3 (approximately 80%) is derived from T_4, through deiodination in peripheral tissues. Levothyroxine serves as an alternate source of T_4 in patients with impaired endogenous production.[2,3]

Pharmacokinetics

Levothyroxine has an oral bioavailability ranging from 40 to 80%. It is absorbed in the intestine, primarily in the jejunum and upper ileum. The presence of food in the gastrointestinal tract decreases absorption. Soybean flour in infant formula, cotton seed meal, walnuts, and dietary fiber may bind levothyroxine and significantly reduce the amount of absorption. Once absorbed, levothyroxine is highly (99.96%) bound to serum proteins, including thyroxine-binding globulin (TBG), thyroxine-binding pre-albumin, and albumin.[2,3]

Levothyroxine is slowly eliminated, primarily by sequential deiodination to T_3 and reverse T_3. The liver serves as the major site for deiodination, but the process also occurs in the kidneys and other tissues. Thyroid hormones are excreted by the kidneys, but may also undergo conjugation with glucuronides and sulfates or be excreted into the bile and gastrointestinal tract to undergo enterohepatic recirculation. The average elimination half-life of levothyroxine is 6 to 7 days. Because of its long half-life, the full therapeutic effect of a dosing change may not be seen for 4 to 6 weeks.[2,3]

Use in Congenital Hypothyroidism

Congenital hypothyroidism occurs in approximately 1:3,000 to 1:4,000 newborns, worldwide. Newborn screening has allowed for earlier diagnosis and institution of treatment, avoiding the impairments in growth and development associated with hypothyroidism.[1,4,5] Several studies have demonstrated the benefit of levothyroxine in these patients. In a 2006 paper published in *Hormone Research*, Marti and colleagues used auditory brain event-related potentials (ERPs) to evaluate neurologic function in 15 children with congenital hypothyroidism (enrolled at the time of diagnosis) and 33 healthy children at 5 years of age.[1] The authors found that the initiation of high dose levothyroxine (mean dose 11.6 mcg/kg/day) within the first

weeks of life resulted in functional anatomical and cognitive organization of the auditory system that did not differ from controls. Based on their findings, the authors concluded that intensive treatment appeared to eliminate abnormal neurologic development in children with congenital hypothyroidism.

Early intervention may also improve cardiac function, another complication of congenital hypothyroidism. In a study of 50 neonates, Mao and colleagues found that levothyroxine significantly improved measurements of left and right ventricular function after just one month of treatment.[6] Dinleyici and colleagues recently described a series of four infants with hypothyroidism associated with Down syndrome who had resolution of their pericardial effusions when levothyroxine was initiated.[7]

Use in Acquired or Transient Hypothyroidism

Thyroid hormone replacement may also be useful in children with acquired hypothyroidism, such as those with cancer,[8] or in infants and children with transient hypothyroidism. Examples of the latter group include preterm infants,[9,10] infants and children in shock who develop sick euthyroid syndrome, and pediatric patients who have undergone cardiac surgery.[11]

Early Use in Autoimmune Thyroiditis

Levothyroxine has also recently been studied as a means of preventing the development of thyromegaly and hypothyroidism in children with autoimmune thyroiditis. In their prospective, randomized, placebo-controlled open-label trial, Karges and colleagues evaluated the effects of levothyroxine in 30 children (mean age 13.3$\pm$2.1 years) with type 1 diabetes and autoimmune thyroiditis.[12] Patients were randomized to receive levothyroxine (average dose of 1.3 mcg/kg/day) or no treatment for 24 months, followed by an additional 6 month observation period. Mean thyroid volume decreased in the treatment group, with a -0.60 standard deviation score (SDS), while it increased in the controls (+1.11 SDS, p=0.0218). Hypothyroidism developed in three treated patients and four controls.

Kordonouri and colleagues found similar results in their study of 15 children (8-17 years of age).[13] Administration of levothyroxine in 7 of the children over a 2 year period resulted in a significantly lower median thyroid volume (-5.3 versus +2.0 SDS in the untreated patients, p=0.032). Both groups of investigators concluded that additional research will be needed to further clarify the benefits of levothyroxine in this condition.

Drug Interactions

There is a long list of drugs that may affect the pharmacokinetics of levothyroxine or its function. In addition, levothyroxine can have a significant impact on many other drugs. Parents of children receiving levothyroxine should be aware of the need to discuss any new prescription or over-the-counter medication, nutritional supplement, or herbal product with their child's health care provider to identify any potential interactions.[2,3]

Several drugs can reduce the oral absorption of thyroid hormones. Oral levothyroxine should be taken at least 4 hours apart from the following agents: antacids containing aluminum or magnesium, calcium carbonate, ferrous sulfate, simethicone, cholestyramine, colestipol, sucralfate, orlistat, or sodium polystyrene sulfonate (Kayexalate®). Drugs affecting protein binding may also alter the effectiveness of levothyroxine. Clofibrate, oral estrogens, methadone, 5-flurouracil, mitotane, and tamoxifen may increase serum TBG, while anabolic steroids, asparaginase, glucocorticoids, and nicotinic acid decrease TBG concentrations. Concurrent administration of levothyroxine and furosemide, heparin, phenytoin, or non-steroidal anti-inflammatory agents may result in displacement of levothyroxine from its protein binding sites, increasing free T_4 levels.[2,3]

Carbamazepine, phenytoin, phenobarbital, and rifampin, increase the metabolism of levothyroxine and may reduce T_4 concentrations by up to 40%. The extent of this effect varies, and dosage adjustment should be guided by thyroid function studies. Several drugs decrease the rate of deiodination of levothyroxine. These agents, amiodarone, beta-adrenergic antagonists, glucocorticoids, and propylthiouracil, may produce only a minimal change in T_4, but result in significant reductions in T_3 levels.[2,3]

Administration of levothyroxine may alter the effects of other drugs. Thyroid hormones increase the catabolism of vitamin-K dependent clotting factors, so that patients receiving warfarin may have an increased pharmacologic response. Warfarin doses should be adjusted to maintain target prothrombin time values and minimize the risk for bleeding.[2,3]

Concomitant use of levothyroxine and selective serotonin reuptake inhibitors, tricyclic, or tetracyclic antidepressants may result in an increased risk of toxicity from both drugs. Use of levothyroxine with antidiabetic drugs or insulin may decrease their effect. Dosage adjustment may be necessary to maintain desired

serum glucose levels. The effect of digoxin may be reduced by administration of levothyroxine. Use of levothyroxine with sympathomimetic drugs may increase the effect of either drug. Use of ketamine with levothyroxine may produce hypertension and tachycardia. Levothyroxine may also reduce the uptake of radiographic agents, including ^{123}I, ^{131}I, and ^{99m}Tc.[2,3]

Use of thyroid hormones with growth hormone may cause premature epiphyseal closure. Patients requiring this combination should be closely monitored for growth and bone formation. Other drugs have been reported to interact with exogenous thyroid hormones, but the mechanism for the reaction has not been clearly established. These drugs: chloral hydrate, diazepam, ethionamide, lovastatin, metoclopramide, 6-mercaptopurine, nitroprusside, para-aminosalicylate sodium, perphenazine, resorcinol, and thiazide diuretics, should be used with caution in patients being treated with levothyroxine.[2,3]

In addition to these drug interactions, there are several drugs that can produce a transient hypothyroidism, resulting in the need for initiating levothyroxine or dosage adjustment in patients already on therapy. Drugs that reduce TSH secretion, such as dopamine or dopamine agonists, glucocorticoids, and octreotide, may produce a temporary reduction in endogenous thyroid hormone production. Likewise, a reduction in T_3 and T_4 may be seen with use of aminoglutethimide, lithium, methimazole, propylthiouracil, sulfonamides, and tolbutamide. Amiodarone and iodide administration may produce either hypo- or hyperthyroidism.[2,3,14]

Adverse Effects

The predominant adverse effects with levothyroxine are signs of hyperthyroidism, including fatigue, palpitations, tachycardia, hypertension, fever, headache, anxiety, irritability, insomnia, flushing, vomiting, abdominal cramps, diarrhea, muscle weakness, tremors, difficulty breathing, heat intolerance, and diaphoresis. Hair loss may occur, but is usually transient.[2,3]

Long-term exposure to elevated T_4 levels may produce cardiac failure, elevated liver function tests, irregular menses, impaired fertility, weight loss, and decreased bone mineral density. In children receiving long-term therapy, there is a risk for impaired growth. Recent studies, however, have shown minimal impact of levothyroxine on growth. Lomenick and colleagues conducted a retrospective study of 68 children (mean age 10.8±3.2 years) with acquired hypothyroidism. Approximately a third of the children had lost weight (mean 2.3 kg) by their second visit; but by their last visit at 2-4 years, there was no significant change in their weight or body mass index (BMI) percentile.[2,3]

Rare serious reactions with levothyroxine include seizures, pseudotumor cerebri, slipped capital femoral epiphysis, craniosynostosis in infants, and premature epiphyseal closure. Hypersensitivity reactions have been reported to the inactive ingredients in levothyroxine products. Symptoms have included urticaria, angioedema, fever, gastrointestinal symptoms, arthralgia, serum sickness, and wheezing.[2,3]

Dosing Recommendations

Levothyroxine is administered as a single daily dose. It is recommended that oral doses be given in the morning on an empty stomach, ideally 30 minutes to 1 hour before breakfast. For older adolescents and adults requiring full replacement, the oral dose is approximately 1.7 mcg/kg/day, with a usual daily dose of 100 to 125 mcg. Doses greater than 200 mcg/day are not typically necessary.[2,3,5]

In newborns, the recommended oral dose is 10 to 15 mcg/kg/day or approximately 25 mcg/day. Infants with cardiac disease should start at a lower dose. In older infants and children, the following table may be used as a guide for the initial dose:

Age	**Dose** (mcg/kg/day)
0-3 months	10-15
4-6 months	8-10
7-12 months	6-8
1-5 years	5-6
6-12 years	4-5
> 12 years/puberty incomplete	2-3
> 12 years/puberty complete	1.7

Parenteral levothyroxine may be administered intramuscularly or intravenously. The initial parenteral dose should be one-half of the oral dose. Further adjustments should be guided by serum thyroid function tests.[2,3,5]

Total or free serum T_4 and TSH should be monitored on a routine basis in infants and children taking levothyroxine. It is recommended that T_4 be maintained in the upper half of the normal range. Serum TSH should be kept below 20 mUnit/L, but may remain elevated in infants with congenital hypothyroidism for a prolonged period after therapy has been initiated. Levels should be obtained at 2 and 4 weeks after the start of treatment, then every 1 to 2 months

during the first year of life. Monitoring should be done every 2 to 4 months in children between 1 and 3 years of age. After that point, the manufacturer recommends that routine monitoring be done every 3 to 12 months.[2,3]

Recent guidelines from the American Academy of Pediatrics, the American Thyroid Association, and the Lawson Wilkins Pediatric Endocrine Society suggest that monitoring every 6 to 12 months is adequate for children with congenital hypothyroidism over 3 years of age in whom previous levels have been satisfactory. The authors also recommend that free T_4 and TSH levels be obtained 4 weeks after any change in levothyroxine dose.[5]

Availability

Levothyroxine is available as Synthroid® (Abbott) as well as a number of generic products. Most manufacturers market a wide variety of tablet strengths to allow for dose titration, including 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg. For infants and young children, the tablets may be crushed and mixed into a small amount of water. It should not be mixed with infant formula or breast milk. An extemporaneous formulation for making an oral suspension is also available.[15] Levothyroxine injection is available in 200 mcg/10 mL and 500 mcg/10 mL vials.[2,3]

Summary

Use of levothyroxine can have a major impact on reducing the long-term consequences of chronic hypothyroidism. It is the mainstay of treatment of congenital hypothyroidism as well as for acquired hypothyroidism associated with other autoimmune diseases or malignancies. It may also play a role in the treatment of transient hypothyroidism associated with prematurity or illness. Further research is needed to establish the benefit of levothyroxine in these settings.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/26/08:

1. Ivermectin (Stromectol®), a broad-spectrum antiparasitic, was added to the Inpatient and Outpatient Formularies.
2. Oxandrolone, an anabolic steroid used to prevent weight loss in burn patients, was added to the Inpatient Formulary.
3. Bendamustine (Treanda®) was added with restriction to patients with B cell malignancies.
4. Rasburicase (Elitek®) was added for the management of uric acid levels in patients with tumor lysis syndrome.
5. Metronidazole gel (MetroGel®), temsirolimus (Torisel®), and certolizumab pegol (Cimzia®) were added to the Outpatient Formulary.

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