ATTACHMENT 2: CLINICAL BACKGROUND

INTRODUCTION

This attachment provides members of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) and the Advisory Committee for Pharmaceutical Science (ACPS) the clinical background for the use of oral levothyroxine sodium products.

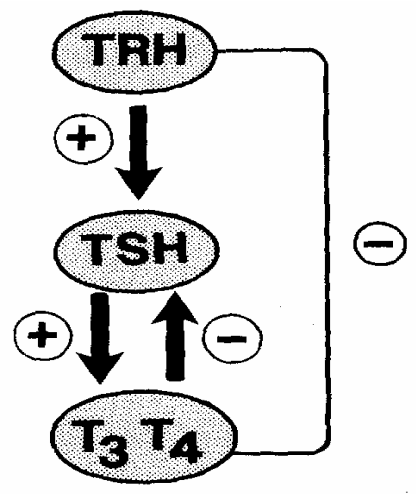
THYROID PHYSIOLOGY, DISEASE STATES, AND USES FOR LEVOTHYROXINE SODIUM

The thyroid gland synthesizes and secretes the thyroid hormones, 3,5,3',5'-thyroxine (T4) and 3,5,3'-triiodothyronine (T3). The majority of thyroid hormone secreted is in the form of T4, a prohormone which is metabolized by peripheral tissues to the active T3. Thyroid hormone has diverse effects on the growth, development, and metabolic processes of many different tissues/organs. For example, it is essential in the normal brain development of the fetus and newborn as well as linear growth and bone development of the growing child. Throughout life, thyroid hormone has profound hemodynamic effects, including alterations in heart rate, cardiac output, and systemic vascular resistance. Thyroid hormone maintains the structural integrity of mature bone; it regulates free water clearance in the kidney; alters lipid metabolism; affects fertility - in effect, thyroid hormone elicits a multitude of biologic responses.

Consequently, thyroid hormone deficiency presents with a wide array of clinical signs and symptoms, as well as laboratory abnormalities that are, in part, related to the magnitude and duration of hormone deficiency and the individual susceptibility of the patient (e.g., presentation during childhood vs. adulthood). While some of these presentations may be considered inconvenient and not life-threatening (fatigue, dry skin, cold intolerance, weight gain), inattention to these mild presentations can result in progression to more severe clinical consequences, such as memory impairment, mental retardation (from untreated/inadequate treatment of congenital hypothyroidism), cardiac dysfunction, and its most severe state, myxedema coma. Conversely, excess thyroid hormone can also result in significant morbidity and mortality including atrial fibrillation or other forms of supraventricular arrhythmias, osteoporosis, and increased risk of fractures.

In order to maintain a euthyroid state, circulating thyroid hormone levels are tightly regulated by the hypothalamic-pituitary-thyroid axis as depicted in Figure 1. Thyroid hormone synthesis and secretion are regulated by the anterior pituitary hormone, thyroid stimulating hormone (TSH or thyrotropin). The secretion of TSH is, in turn, regulated by the hypothalamic hormone, thyrotropin-releasing hormone (TRH). The hypothalamic-pituitary-thyroid axis responds to circulating T4 and T3 levels such that under normal circumstances, elevated thyroid hormone levels provide a ‘negative feedback’ that inhibits the secretion of the hypothalamic and pituitary hormones, while decreased thyroid hormone levels will stimulate the production and secretion of TRH and TSH.

Figure 1. Hormone Interactions in the Hypothalamic-Pituitary-Thyroid Axis



Hypothyroidism is a relatively common disorder with the overwhelming majority of cases due to primary thyroid gland failure secondary to autoimmune destruction of the gland (Hashimoto's thyroiditis). Other etiologies include trauma, surgery, radioablation, drug-induced, and infections. The diagnosis is often made based on clinical signs and symptoms that are confirmed with laboratory measurements of TSH and thyroid hormone levels. Once diagnosed, patients require thyroid hormone replacement therapy. In the majority of cases, replacement therapy is life-long.

NARROW RANGES FOR THERAPEUTIC DOSING

The aim of thyroid hormone replacement therapy is to ensure an adequate supply of the missing hormone to correct the clinical symptomatology of hypothyroidism and normalize thyroid function laboratory tests. The preferred form of thyroid hormone therapy is with levothyroxine sodium, with adults requiring approximately 1.6 mcg/kg/day whereas children may require higher amounts, up to 4 mcg/kg/day. Older patients or patients with underlying cardiac disease should be initiated on therapy with lower doses and slow, careful upward titration to the full replacement dose. Starting doses in these patients are typically 25 mcg to 50 mcg daily with monitoring to ensure that cardiac disease is not exacerbated. The availability of sensitive TSH assays with lowest reliable measurements values of 0.02 mIU/L or less and serum free T4 assays has allowed physicians to monitor and carefully dose titrate patients while avoiding over- or under-replacement. The clinical consequences of suboptimal dosing are similar to what has been described above regarding thyroid hormone deficiency or excess states. Laboratory monitoring after initiation of replacement therapy should not take place until drug levels reach steady state (generally 6 weeks) with any necessary dose adjustments requiring follow-up lab assessments. Once an appropriate replacement dose has been established, routine clinical and laboratory evaluations (every 6 to 12 months) are important to ensure maintenance of safe and effective dosing. More frequent assessments may be necessary in neonates, patients with underlying heart disease, during pregnancy or when certain drugs are initiated or discontinued. All in all, levothyroxine sodium is considered a drug with a narrow therapeutic index in which suboptimal dosing may result in untoward side effects.

Other thyroid conditions or diseases in which levothyroxine sodium is utilized include thyroid cancer and thyroid nodules. Similar concerns regarding appropriate dose selection, laboratory monitoring, and careful dose titration apply for the management of these patients. However, a notable difference that merits consideration by the scientific community is the target goal of TSH levels in patients receiving levothyroxine sodium as suppressive NOT replacement therapy. Differentiated thyroid cancers express the TSH receptor and respond accordingly to TSH stimulation with an increased rate of cell growth. TSH suppressive therapy refers to use of levothyroxine sodium at supraphysiologic doses to achieve TSH levels within a more narrow range than is targeted with replacement therapy in order to prevent thyroid

cancer cell growth. Depending on the histology, tumor size, and presence of local or distant metastases, the TSH level targeted may be < 0.1 mIU/L for the high-risk patients or at or below the lower limit of normal (0.1-0.5 mIU/L) for low-risk patients. It should be apparent that achieving goals within this tight range while avoiding the consequences of suboptimal treatment (thyrotoxicosis from over-treatment vs. cancer growth from under-treatment) requires fine precision in levothyroxine sodium dosing. While high-quality levothyroxine sodium products are desirable in any patient population, it is especially critical in the treatment of differentiated thyroid cancer.

CONCLUSIONS

The diagnosis and management of thyroid disorders have advanced significantly over the past century. Alongside these achievements in clinical and laboratory medicine have been the significant improvements in the source of thyroid hormone for replacement therapy – evolving from crude extracts of animal thyroid glands to more purified synthetic thyroid hormones. Today, as a result of FDA's 1997 Federal Notice and our application approval standards (see Attachment 1 of this memorandum), FDA-approved levothyroxine sodium products are less variable than those that were historically available. As explained above, because levothyroxine sodium is a narrow therapeutic index drug, it is critical that patients be dosed precisely.

REFERENCES

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