Is Parenteral Levothyroxine Therapy Safe in Intractable Hypothyroidism?

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Abstract: Case: A 32-year old woman was admitted to the hospital due to intractable hypothyroidism refractory to high dose of oral L-thyroxine therapy. She underwent total thyroidectomy and radioactive iodine therapy due to papillary thyroid cancer. After excluding poor adherence to therapy and malabsorption, levothyroxine absorption test was performed. No response was detected. Transient neurologic symptoms developed during the test. She developed 3 attacks consisting of neurologic symptoms during high dose administration. The patient was considered a case of isolated L-thyroxine malabsorption. She became euthyroid after intramuscular twice weekly L-thyroxine therapy.

Discussion: There are a few case reports regarding isolated L-thyroxine. We report successful long term results of twice weekly administered intramuscular L-thyroxine therapy. We also draw attention to neurologic side effects of high dose L-thyroxine therapy.

Abbreviations: BMI, body mass index; CT, computed tomography; FT4, free thyroxine; IHH, idiopathic intracranial hypertension; LT4, levo-thyroxine; RAI, radio active iodine; TFT, thyroid function tests; TIA, transient ishemic attack; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone

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INTRODUCTION

Primary hypothyroidism is a common disorder mostly due to autoimmune or surgical reasons. It is managed easily with a single daily oral dose of 1.6−2.4 μg/kg levothyroxine (LT4).[1,2] It is poorly absorbed (48−80%) from upper gastrointestinal system even under optimal conditions.[3,4] There are numerous factors affecting LT4 absorption.[3,4] Absorption rate may decrease with age and varies between different preparations by 10−15%.[3] Compliance to therapy is defined as regular dosing and ingesting on an empty stomach at least 30 min before breakfast in the morning and at least 6 h of fasting.[3−5] Poor adherence to therapy is the major cause of high doses.[3−17] Simultaneous ingestion of some foods and drugs and certain diseases may impair absorption of LT4 via different mechanisms[3−17] (Table 1). Higher doses of LT4 can overcome malabsorption.[3−17]

We present a case of isolated malabsorption of thyroxine who responded intramuscular LT4 therapy and developed neurologic symptoms after administration of high doses.

CASE

A 32 year old female patient was admitted to endocrinology ward in 2008 due to fatigue, progressive weight gain (71 kg in 4 years), dry skin, and hair and eyebrow loss. The patient had undergone total thyroidectomy for thyroid papillary cancer 1.2 cm in size in 2004 and received radioactive iodine (RAI) therapy. She was on 400 μg LT4 therapy with a thyroid stimulating hormone (TSH) level of 98.22 mIU/L.

On physical examination blood pressure was 100/70 mmHg, heart rate 72 bpm with regular rhythm, body temperature 36 °C, body mass index (BMI) 38.3 kg/m^2, non-pitting edema on lower extremities, and lessened deep tendon reflexes. She denied co-administration of any drugs or herbal products that might interfere with LT4 absorption. She was consulted with psychiatrist and no psychiatric disorder was detected.

LT4 at a dose of 400 μg/day was administered on an empty stomach 30 min before breakfast and under supervision of a nurse. No changes were observed in thyroid function tests (TFT) after 7 days. Clinical and laboratory investigations eliminated liver and pancreas diseases, congestive heart failure, and pregnancy. Neither diarrhea nor steatorrhea was present. Stool was negative for parasites. Upper gastrointestinal endoscopy did not yield any pathology and the gastroenterologist refused to take biopsy. Vitamin B12 level was normal without therapy and intrinsic factor was negative. Antibodies against endomysium, tissue transglutaminase, TPO, and thyroglobulin were negative. Triiodothyronine was added to high dose LT4 therapy, but there was no improvement after combination therapy was commenced.

Table 1. Foods, drugs and diseases impairing levothyroxine absorption.

Walnuts	Phenobarbital
Soybeans	Raloxifene
Dried prunes	Cholestyramine
Coffee	Ferrous sulfate
Grapefruit juice	Sodium polystyrene sulfonate
Proton pump inhibitors	İnflammatory bowel disease
Carbamazepine	Lactose intolerence
Sevelamer	Liver diseases
Orlistate	Pancreas diseases
Biphosphonates	Coeliac disease
Calcium carbonate	Small intestine surgeries
Antacids	Congestive heart failure
Phenytoin	Giardiasis
Rifampicin	Intestinal infections

LT4 absorption test was carried out with orally administered 1000 μg LT4. Serum free T4 and TSH levels were measured with 2-h intervals during 6 h test. However the levels did not change (Table 2). At the 5th hour of testing, the patient developed aphasia, loss of vision, and hemiparesis. Cranial imaging was normal and she was diagnosed with transient ischemic attack (TIA) by the neurologists. The symptoms disappeared by the 5th day of anti-oedema and acetylsalicylic acid therapy. Since there was no response to high dose oral LT4, parenteral LT4 therapy was planned. The patient was discharged on oral 450 μg LT4 plus 75 μg triiodothyronine combination therapy until provided from abroad.

She was lost follow-up until November 2012. Meantime she gained 27 kg more since first visit in 2008 (98 kg since thyroidectomy), was diagnosed with hypertension, and suffered from prolonged menstrual bleeding. 500 μg LT4 had been administered intravenously for 2 h in 2011 in another health facility. On the 2nd day of intravenous therapy she developed a hypertensive attack (220/140 mmHg) accompanying mild left hemiparesis, dysarthria, and paresthesia around her mouth. The attack resolved uneventfully within a few days and cranial imaging had been normal again. She could not tolerate rectal and vaginal route of administration. Starting with 200 μg/day intramuscular LT4 (L-thyroxin® Henning inject, Henning, Berlin, Germany) was escalated at weekly intervals (500, 1000, and 1200 μg). Serum free thyroxine (FT4) and TSH levels were measured during escalation of doses (Figure 1). Twenty four hours after starting 1200 μg, she experienced left-sided loss of strength. Cranial imaging studies were normal again. The symptoms regressed within a week. The laboratory studies including blood count, biochemical measurements, prothrombin time, partial thromboplastin time, fibrinogen, D-dimer, protein C, protein S, antithrombin III, lupus anticoagulant, and homocysteine were found to be within normal values. She did not have mutations in factor II and V but a heterogeneous PAI-1 mutation was detected.

Table 2. FT4 and TSH levels after administration of oral 1000 μg L-thyroxine.

	Baseline	2nd hour	4th hour	6th hour
FT4 (ng/dL)	0.40	0.40	0.40	0.40
TSH (mIU/L)	100	81.81	84.74	93.48

FT4: Free thyroxine, TSH: Thyroid stimulating hormone.

Therapy was switched to another regime consisting of 500 μg LT4 by intramuscular route twice a week. Neurologic symptoms did not appear. Serum TSH and FT4 levels quickly reached the reference range (Figure 2), and the symptoms related to hypothyroidism improved. Based on the postulation that prolonged hypothyroidism may cause malabsorption due to oedema, oral LT4 therapy was commenced again following improvement in TFT. However soon after oral therapy was started, hypothyroidism and associated laboratory findings ensued again. Therefore therapy was switched to the previous regime again (intramuscular 500 μg L-thyroxine twice a week).

During the first year of parenteral therapy fatigue and depressive symptoms improved, she lost 98 kg in total, regular menses resumed, anemia and dyslipidemia improved without any intervention. At last visit TSH was 0.16 mIU/L, FT4 1.35 ng/dL, and thyroglobulin <0.2 ng/mL.

DISCUSSION

The mechanism of translocation of LT4 across the mucosa is still obscure. Most of the data regarding LT4 absorption are derived from animal studies.[3,18] A scarcely few number of human studies support the animal data.[3,18] In studies involving radioiodinated T4 fecal tracer excretion methods, it was shown that the most active absorption sites for T4 are proximal and mid jejunum.[3,18] Enterohepatic circulation of endogenous T4 is not robust and finely tuned adjustments can be made according to T4 production rate.[3,18] However in hypothyroid patients and patients using drugs affecting bile acid secretion and sequestration, this pathway becomes more important and it is required to make an increase in LT4 dosage.[3,18]