

The difficult patient: drug interaction and the influence of concomitant diseases on the treatment of hypothyroidism

O paciente difícil: interação entre drogas e influência de doenças concomitantes no tratamento do hipotireoidismo

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SUMMARY

Although most hypothyroid patients do well with one single tablet of thyroxine daily, approximately 10% are dissatisfied and another important group of patients is difficult to control. We reviewed the most common causes for frequent-dose adjustment or high-dose requirement, including poor compliance with therapy and inadequate medication. Since these two causes have been ruled out, drug interaction and other concomitant diseases need to be investigated. Requirements of thyroxine increase in all conditions characterized by impaired gastric acid secretion. Proton-pump inhibitors, antacids and a long list of drugs may decrease thyroxine absorption. In addition, a series of diseases including celiac disease and chronic inflammatory intestinal diseases, as well as nutritional habits may be important in patient control. Finally, we mention the effects of a growing list of drugs and thyroid disruptors that may also affect thyroid hormone metabolism at many levels. *Arq Bras Endocrinol Metab.* 2010;54(5):435-42

Keywords

Medication-taking behavior; compliance; bioequivalence; absorption; nutritional habits

SUMÁRIO

Embora a maior parte dos pacientes com hipotireoidismo fique bem com um único comprimido diário de tiroxina, aproximadamente 10% não ficam satisfeitos e outro importante grupo de pacientes apresenta controle difícil. Foram revistas as causas mais comuns para necessidades frequentes de ajuste de dose ou uso de dose elevadas, incluindo falta de adesão à terapia e medicação inadequada. Descartando-se essas duas causas, é necessário investigar o uso de drogas e a presença de doenças concomitantes. Existe necessidade maior de tiroxina quando diminui a secreção ácida do estômago. Inibidores de bomba de prótons, antiácidos e uma longa lista de drogas podem dificultar a absorção da tiroxina. Várias doenças, incluindo a doença celíaca e as doenças intestinais inflamatórias crônicas, além dos hábitos alimentares, são importantes no controle do paciente hipotiroideo. Finalmente, foram mencionados os efeitos de uma lista crescente de drogas e disruptores que podem afetar o metabolismo tiroídiano em diferentes níveis. *Arq Bras Endocrinol Metab.* 2010;54(5):435-42

Descritores

Comportamento; adesão; bioequivalência; absorção; hábitos alimentares

INTRODUCTION

Thyroid hormone therapy is often rewarding, simple and inexpensive. Most patients are satisfied with one single tablet of synthetically derived levothyroxine daily. Once the dosage has been adjusted to give opti-

mal clinical response and normal serum TSH, the replacement dosage often remains stable for years. However, nearly 10% of the patients are not satisfied and another important part of our patients is not well controlled and needs unusually high doses of thyroid hormone replacement (1). Why would this happen?

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A series of recent publications have been pointing to genetic polymorphisms in deiodinases and thyroid hormone transporters as the main causes of dissatisfaction. Common germline genetic variations are probably responsible for the relatively wide range of serum thyroid hormone levels observed in the normal population and may also be involved in the differential bioavailability of thyroid hormones in different tissues (2). However, this review does not focus on the dissatisfied patient, but on the patient who is difficult to control.

COMPLIANCE WITH THERAPY AND MEDICATION-TAKING BEHAVIOR

The causes for frequent-dose adjustment or high-dose requirement are, in general, prosaic. The most common cause is poor compliance with therapy and medication-taking behavior. This issue is relevant for the management of all chronic asymptomatic or oligosymptomatic diseases, such as diabetes, hypertension and other diseases in which no immediate physical symptoms result from such behavior (3). One day's tablet represents 24% of the weekly dose and, because of the long half-life of thyroxine, the influence of missing a day on thyroid hormones and TSH levels will manifest over several days. A recent publication involving a large number of Canadian elders who had received a new prescription for an antihypertensive agent demonstrated that persistence at 1 year dropped 50-60% (4). The authors found that compliance was greater in women, patients of higher socioeconomic status, and younger individuals, with lower burdens of comorbidities (4). Unfortunately, most of our patients do not fulfill this profile.

Confirming other data on the subject, we published a compliance study comprising 100 patients from public hospitals in Campinas and Rio de Janeiro, who presented persistently elevated TSH levels despite increasing the levothyroxine dose (5). Our poor compliance rate was similar to that seen in literature: 82% of the patients. Sixty two percent of the patients had a poor medication-taking behavior mostly because they forgot or neglected to take their pills, but 12% of these patients complained about intolerance or side effects and 8% claimed they could not afford to buy the medication (5). Levothyroxine is allegedly supplied at our primary care institutions, but unfortunately this supply is not regular. Subsequently, we supplied one of the four preparations containing levothyroxine commer-

cially available at that time, reinforced the importance of the medication by giving lectures to the patients, and undertook a simple pill counting control compliance measure. All patients were controlled after one month with all four preparations; however, the most important finding of our trial was that 18% of these patients, after just one month of adequate medication-taking, were hyperthyroid. Indicating they had already been prescribed a levothyroxine dosage higher than they were really in need of. And, certainly, the fact that they became hyperthyroid when they started to take their pills appropriately represents a risk. None of our patients had any cardiac symptom or complained of any problem, but they could have had serious problems especially considering that most of these patients were elderly and presented comorbidities.

Excluding poor medication-taking behavior is usually a difficult task. After exhausting every usual measure for compliance such as pill counting, counseling methods, motivational interviewing and problem solving treatment, a clinical test to estimate levothyroxine absorption may be proposed. The test consists of a single large dose of thyroxine administration, usually 1,000 mcg, and then monitoring serum T4 levels over time (6). Unfortunately, there are no well-established standards for this test. Even though it indicates that the patient absorbs thyroxine when exposed to a large dose, it does not rule out impairment of normal dose absorption. Moreover, the test does not quantify the absorption impairment caused by the edema produced by the hypothyroidism on the small bowel mucosa. Hence, simply increasing the levothyroxine dose may have the same practical effect of submitting the patient to the single dose test, with the advantage of treating him.

ADEQUACY OF MEDICATION

Once poor-medication is discarded and before considering drug interaction and concomitant diseases, it is necessary to check if the patient medication is adequate. It is important to remember that certain conditions may physiologically require higher doses of thyroid hormone replacement, such as pregnancy or childhood (Table 1).

Obesity may also be a cause of a higher levothyroxine requirement. In fact, individual levothyroxine requirements are more related to the lean body mass than to the total body weight (7). On studying more than 27 thousand Norwegians without previously known

Table 1. Causes of high-dose thyroid hormone replacement

Poor medication-taking behavior/compliance
Adequacy of medication: pregnancy, infancy/adolescence, obesity
Drug interaction
Concomitant diseases
Type 2 deiodinase polymorphisms/ thyroid hormone transporters

thyroid disease, Asvold and cols. (8) proved that low thyroid function was associated with high body mass for men and women (8). Two hypotheses have been proposed to explain the relation of thyroid function with body mass. The first one involves the effect of leptin and other adipokines (9), which is favored by the following facts: weight reduction in obese individuals may be associated with reduced thyroid function (10,11), and patients with anorexia nervosa who gain weight have increased thyroid function (12). The second hypothesis suggests that low thyroid function may lead to obesity, probably reducing basal metabolic rate (13).

Requirement also seems to be associated with hormonal status. Studying 50 patients after thyroidectomy, Jackeline Jonklaas (14) found that the weight-based levothyroxine dosage required to normalize TSH was 1.7 mcg/kg in both sexes; however, premenopausal women appeared to have a greater dosage requirement than both postmenopausal women and men (14). Of course, dose requirements are also age-dependent, possibly because of the combination of weight loss, lean mass loss and decreased clearance of T4 (14,15).

Another very common problem is that the patient may be using an inadequate preparation or a preparation with no bioequivalence. Levothyroxine is a narrow therapeutic range drug for which precise and consistent dosing are essential, particularly in the elderly and in high-risk thyroid cancer patient treatment. It is not unusual to see patients using “natural medicines” that do not contain appropriate doses of the active principals, formulas or manipulated preparations that lack a proper control. There are different brand-name and generic levothyroxine products being manufactured in Brazil and many patients switch from one to another at their convenience or at the pharmacist’s or relatives’ advice, frequently without the prescribing physician’s knowledge. Generic levothyroxine is considered equivalent to the brand names and, because there is a cost differential between generic levothyroxine and many of the brand name products, physicians and patients have been turning to generic levothyroxine. However, the

re is considerable concern on the bioequivalence standards for levothyroxine product comparisons (9) and the American Thyroid Association (ATA), along with the American Association of Clinical Endocrinologists (AACE), and The Endocrine Society (TES) have endorsed a joint statement expressing concern about the flawed methodology used to determine bioequivalence and the potential harm it could bring to patients (16). In fact, there have been a series of adverse event reports (17). Patients should be alerted that they will be required to perform additional blood tests and dose adjustments after switching preparations.

DRUG INTERACTION AND CONCOMITANT DISEASES

If the patient was correctly diagnosed, poor medication-taking or compliance issues were discarded, and the dose prescribed is adequate, you may be facing a drug interaction problem or a concomitant disease that impairs levothyroxine’s proper absorption or action (Table 2).

Table 2. Causes of impaired levothyroxine absorption

Drugs	
Proton-pump inhibitors (PPI)	Calcium salts
Aluminium, magnesium hydroxide	Calcium carbonate
Sucralfate	Orlistat
Ion exchange resins	Cation exchange resins
Ferrous sulfate	Bile acid sequestrants (Cholestyramine; Colestipol)
Diseases	
<i>Helicobacter pylori</i> infection	Celiac disease
Atrophic gastritis	Short bowel syndrome
Giardiasis and other parasitic diseases	Lactose intolerance
Other intestinal chronic inflammatory diseases	
Nutritional habits	
Coffee	Juice
Cereals	Other foods

The absorption of levothyroxine occurs within an interval of 3 hrs of ingestion, mainly in the jejunum and ileum (18-20). On average, approximately 70%-80% of the available tablet dose is absorbed by the euthyroid individual, and this absorption rate may diminish in the hypothyroid patient (18). Absorption is maximal when the stomach is empty, reflecting the importance of gastric acidity in the process (21,22). In fact, the comple-

xity of the acid producing machinery in the stomach may contribute to the individual variability observed in daily thyroxine requirement in a longitudinal evaluation (23).

There is an increase in the requirement of oral thyroxine in all conditions characterized by impaired gastric acid secretion, which is more pronounced in adult patients presenting with atrophic gastritis and concomitant *H. pylori* infection, who have severe hypochlorhydria (24). In an attempt to reduce the size of their goiters or at least to minimize further growth, Centanni and cols. (21) treated 248 multinodular goiter patients with levothyroxine (21). The dose was progressively increased until a low serum thyrotropin level (0.05 to 0.20 mU per liter) was reached. There were 113 patients with multinodular goiter and impaired gastric acid secretion. Fifty-three had *H. pylori*-related nonatrophic gastritis and 60 patients had atrophic gastritis. The authors observed that patients with atrophic gastritis required an increase of 27% in the thyroxine dose, whereas patients with *H. Pylori* non-atrophic gastritis required an increase of 22% in their dose. Interestingly, there was an additive effect: patients with both *H. pylori* and atrophic gastritis needed a 34% higher dose of T4. Although the clinical importance of these findings is fairly clear, the mechanism by which intestinal absorption of thyroxine is impaired in patients with hypochlorhydria is unknown. We may only speculate that oral thyroxine is administered as sodium salt, which is less lipophilic than the native hormone, which enters target cells both through passive diffusion and in a carrier-mediated, inhibitable way (25,26). In this respect, achlorhydria due to atrophic gastritis (27,28) and ammonia production, or both, which are characteristic of *H. pylori* infection (29,30) may alter the ionization status and the conformational characteristics of the thyroxine molecule and thus, the efficiency of intestinal absorption of the hormone.

It is important to remember that atrophic gastritis and serum parietal-cell antibodies are associated with Hashimoto's disease and serum thyroid peroxidase antibodies. Therefore, patients with Hashimoto's disease are more susceptible to present a concomitant autoimmune atrophic gastritis. And, of course, many individuals with atrophic gastritis and parietal-cell antibodies also present *H. pylori* infection (21).

Among the 248 multinodular goiter patients treated with thyroxine by Centanni and cols. (21), there were 11 patients diagnosed with *H. pylori* who were

treated for this infection. TSH levels measured before and after *H. pylori* eradication demonstrated a clear effect of gastric infection on the absorption of thyroxine impairment, an effect that has been proved by others too (21,31). In *H. pylori* infection, bacterial production of urease neutralizes gastric pH, impairing the absorption of many drugs (31). Other 10 patients with multinodular goiter and gastroesophageal reflux disease, who were treated with both thyroxine and omeprazole, had their serum thyrotropin levels evaluated before and after treatment. Omeprazole has also got an important effect *per se*, probably because it causes hypochlorhydria, likewise all proton-pump inhibitors (PPI) do (21,32). In conclusion, *H. pylori* infection and hypochlorhydria should be considered when prescribing any drugs for which absorption is potentially affected by intragastric pH.

In addition to PPI, antacids also impair levothyroxine absorption. There are other commonly used drugs that impair intestinal absorption such as ion exchange resins, bile acid sequestrants, and sucralfate, which have the same effect. Ferrous sulfate, frequently used to treat anemia, may impair thyroxine as well as orlistat absorption, a drug that works by interfering with the action of gastrointestinal (GI) lipase in the GI tract, and calcium (33). There is an increasing number of drugs that have been reported to affect levothyroxine absorption (33) (Table 2).

Furthermore, a series of other diseases can impair levothyroxine absorption as well. Celiac disease is worth the mention. In fact, likewise atrophic body gastritis, celiac disease and other autoimmune conditions, including inflammatory small bowel disease, are frequently associated with autoimmune thyroiditis (34,35), which in turn consists in the main cause of hypothyroidism in adult patients (36). Celiac disease may have mild or subtle symptoms, and there is a case report in which resistant hypothyroidism appeared to be the only major manifestation of the disease (37). The patient improved after a gluten-free diet was introduced (37).

Bariatric surgery and all surgeries that reduce gastrointestinal absorption surface may also impair thyroxine absorption (38). It is especially relevant to remember that certain parasitic diseases may be an important cause of malabsorption in underdeveloped countries. There is a report of a severe case of hypothyroidism reputed to have been caused by an intestinal giardiasis (39). Other causes of malabsorption may include lactose intolerance (40).

Cardiovascular diseases deserve a special consideration concerning thyroid hormone administration. We all fear the potential detrimental effects of thyroid hormone administration in a variety of clinical settings. Indeed, high doses of thyroxine can cause cardiac ischemia, even in the absence of significant coronary artery disease; increase oxygen demand, coronary spasm and arrhythmias (41). For this reason, levothyroxine is introduced in very small doses, in general, half of the 25 mcg tablet in patients with cardiovascular diseases. Increases in dosage are also made very cautiously and slowly and, many times, we are tempted to maintain the patient in a state of subclinical hypothyroidism. However, experimental data suggest that thyroid hormones improve myocardial functions, increase capillary flow and induce angiogenesis after myocardial infarction (42-48). In fact, thyroid hormone administration shows inotropic and antiarrhythmic properties and reduces the risk of death after and some clinical conditions such as chronic congestive heart failure (42), organ transplantation (43,44), coronary artery (45) and cardiopulmonary bypass (46), myocardial ischemia (47) and in prolonged critical illness (48). Consequently, it is important to always aim at a target TSH in the normal range for the patient's age, especially if the patient has a cardiovascular disease. Also, it is important to remember that congestive heart failure is associated to altered morphology, permeability, and absorption of the digestive tract (49).

NUTRITIONAL HABITS

Nutritional habits are also very important to control hypothyroid patients (Table 2). Most of the active components of a thyroxine pill are absorbed within the first 20-30 minutes after ingestion, although completion of absorption takes three hours. Therefore, it is recommended to obey a 30-minute interval between thyroxine pill ingestion and breakfast. A series of reports have demonstrated that coffee, especially espresso coffee, impairs thyroxine absorption (50). Dietary fibers appear to have a smaller, but still significant effect on thyroxine absorption (51). Grapefruit juice and probably other citric fruits might also impair thyroxine absorption (52).

OTHER DRUGS THAT INTERACT WITH THYROXINE

In addition to drugs that cause impairment in thyroxine absorption, there are other drugs that interact with

thyroxine. Although they are not the scope of this review, it is worth mentioning that there are drugs that may increase hepatic metabolism and cause hypothyroidism (carbamazepine, hydantoins, phenobarbital, rifampin); that may cause a decrease in thyroid hormone secretion and, therefore, cause a higher dose requirement of thyroxine (aminoglutethimide, amiodarone, iodide-including and iodine-containing radiographic contrast agents, lithium, methimazole, propylthiouracil, sulfonamides, tolbutamide); that may decrease T4 5'-deiodinase activity (amiodarone, beta-adrenergic antagonists: propranolol > 160 mg/day, glucocorticoids: dexamethasone \geq 4 mg/day, propylthiouracil); that may increase serum TBG concentration (estrogen, clofibrate, heroin/methadone, mitotane, tamoxifen); that may decrease serum TBG concentration (androgens/anabolic steroids, glucocorticoids, nicotinic acid, asparaginase); that may cause protein-binding site displacement (furosemide: > 80 mg IV, heparin, hydantoins, nonsteroidal anti-inflammatory drugs: fenamates, phenylbutazone, salicylates > 2 g/day). A series of other drugs need attention because, through unknown or complex mechanisms, they may interfere with thyroxine therapy; antidiabetic agents: biguanides, meglitinides, sulfonylureas, thiazolidinediones, insulin; antidepressants: tricyclic (e.g., amitriptyline), tetracyclics (e.g., maprotiline), selective serotonin reuptake inhibitors (SSRIs; e.g., sertraline); growth hormones: somatrem, somatropin; oral anticoagulants: coumarin derivatives, indandione derivatives; cytokines: interferon- α , interleukin-2; others: ketamine, sympathomimetics, cardiac glycosides, chloral hydrate, diazepam, ethionamide, lovastatin, metoclopramide, 6-mercaptopurine, nitroprusside, para-aminosalicylate sodium, perphenazine, resorcinol (excessive topical use), thiazide diuretics.

Interestingly, some agents, such as amiodarone and iodide may cause both hypo- and hyperthyroidism (53,54). Amiodarone is a drug very frequently used in Brazil. We have a 10-million Chagas disease population and amiodarone is a very potent and effective antiarrhythmic drug. It is a benzofuran-derived, iodine-rich compound with some structural similarity to thyroxine (T4). Amiodarone contains approximately 37% iodine by weight. Each 200-mg tablet is estimated to contain approximately 75 mg of organic iodide, 8%-17% of which is released as free iodide. Standard maintenance therapy with 200 mg amiodarone can provide more than 100 times the daily iodine requirement. Amioda-

rone causes a wide spectrum of effects on the thyroid (53,54). In a study of 81 Chagas disease patients using amiodarone, we found that 21% of the patients had elevated TSH levels and 8% low TSH levels (55). Amiodarone may also decrease T4 deiodinase activity. Likewise propranolol, dexametasone and PTU may decrease T3 levels. Although usually normal, serum T4 levels may occasionally be slightly increased. In patients treated with large doses of propranolol (> 160 mg/day), T3 and T4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T3 concentrations by 30%, with minimal change in serum T4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T3 and T4 levels due to decreased TBG production.

Since many of our hypothyroid patients are also diabetic, we should remember the TSH-lowering effect of metformin (56).

Finally, we need to mention the effects of a growing list of thyroid disruptors that may also affect thyroid hormone metabolism at many levels (57) (Table 3).

An increasing amount of toxic substances has been described, many of which we still do not fully understand

how they affect thyroid hormones. For instance, a study of 42 healthy non-smoker petrol filling workers from India found a significant toxic effect on workers exposed for longer duration who presented lower TSH levels. However, whereas their serum T3 levels dropped, T4 and free T4 levels augmented (58). The effects of thyroid disruptors are complex and still difficult to interpret. They may account for a part of the patients who we are convinced that are compliant, adequately medicated and do not present any absorption impairment, but have a hard time controlling their hypothyroidism.

In conclusion, the patient difficult to control most frequently is not compliant or was not adequately diagnosed/prescribed. Indeed, the majority of our patients fit this profile and become adherent to therapy after a few good conversations. In some patients, however, we need to exclude concomitant disease and drug interaction. Eventually, in the rare cases in which all these issues were discarded, we remain with the hypothesis of the presence of thyroid disruptors, deiodinase or thyroid hormone transporter polymorphisms leading to higher dose requirements and we just adjust thyroxine dose. Treating the hypothyroid difficult patient may not be so difficult, after all.

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Table 3. Thyroid disruptors: clinical effect and putative mechanism. Notice that some products have several toxic effects

Xenobiotic product	Clinical effect on thyroid metabolism	Putative mechanism
Perchlorates, thiocyanate, nitrate, phthalates, bromates	Decreases synthesis of T3 and T4	Blocking iodide uptake into thyroid cell
Soy, isoflavones, methimazole, benzophenone 2 (pesticide), amitrole (pesticide)	Decreases synthesis of T3 and T4	Blocking TPO production into thyroid cell
PCBs, pentachlorophenol, flame retardants, phthalates	Possible effect on fetal brain T4 production and brain development	Compete to thyroid transport protein
Dioxin, PBDE, chlordane (pesticide)	Increase biliary elimination of both T4 and T3	Alter transport across cell membrane
Acetochlor (herbicide)	Increase biliary metabolism of both T4 and T3	Enhance hepatic metabolism
Triclosan, PCBs, dioxin, difuran, pentachlorophenol (pesticide)	Decrease sulfation of thyroid hormones and possibly decrease peripheral T3 synthesis	Inhibit sulfation
PCBs, octyl methoxycinnamate, FD&C red dye	Decrease peripheral T3 synthesis	Inhibit deiodinase activity
DDT, PCBs	Decrease T3 and T4 production	Inhibit TSH receptor

Polychlorinated biphenyls (PCBs) were commonly used as stabilizing additives in the manufacture of flexible PVC coatings for electrical wiring and electronic components to enhance the heat and fire resistance of the PVC.

Perchlorates are used extensively within the pyrotechnics industry, and ammonium perchlorate is also a component of solid rocket fuel.

Thiocyanate is used as a precursor for the synthesis of pharmaceuticals and other specialty chemicals.

Dioxins are the by-products of various industrial processes (i.e., bleaching paper pulp, and chemical and pesticide manufacture) and combustion activities (i.e., burning household trash, forest fires, and waste incineration).

Bromates are formed many different ways in municipal drinking water.

Phthalates are mainly used as plasticizers (substances added to plastics to increase their flexibility, transparency, durability, and longevity).

Difuran is used in the elaboration and/or manufacturing of flavor and fragrance agents.

Octyl methoxycinnamate is a component used in some sunscreens and lip balms.

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