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DRUG-INDUCED HYPOTHYROIDISM

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Abstract The thyroid axis is particularly prone to interactions with a wide variety of drugs, whose list increases year by year. Hypothyroidism is the most frequent consequence of drug-induced thyroid dysfunction. The main mechanisms involved in the development of primary hypothyroidism are: inhibition of the synthesis and/or release of thyroid hormones, immune mechanisms related to the use of interferon and other cytokines, and the induction of thyroiditis associated with the use of tyrosine kinase inhibitors and drugs blocking the receptors for vascular endothelial growth factor. Central hypothyroidism may be induced by inhibition of thyroid-stimulating hormone (bexarotene or corticosteroids) or by immunological mechanisms (anti-CTLA4 or anti-PD-1 antibody drugs). It is also important to recognize those drugs that generate hypothyroidism by interaction in its treatment, either by reducing the absorption or by altering the transport and metabolism of levothyroxine. Thus, it is strongly recommended to evaluate thyroid function prior to the prescription of medications such as amiodarone, lithium, or interferon, and the new biological therapies that show important interaction with thyroid and endocrine function in general.

Key words: thyroid, hypothyroidism, drugs

Resumen ***Hipotiroidismo inducido por drogas.*** El eje tiroideo es particularmente proclive a sufrir interacciones con una amplia variedad de drogas, cuya lista se acrecienta año a año. El hipotiroidismo es la consecuencia más frecuente de disfunción tiroidea inducida por fármacos. Los principales mecanismos involucrados en el desarrollo de hipotiroidismo primario son: la inhibición de la síntesis y/o liberación de las hormonas tiroideas, mecanismos inmunes relacionados con el uso de interferón y otras citoquinas, y la inducción de tiroiditis asociada al uso de los inhibidores tirosina-kinasa y a drogas bloqueantes del receptor del factor de crecimiento del endotelio vascular. El hipotiroidismo central puede ser inducido por la inhibición de la tirotrofina (bexaroteno o corticoides) o por mecanismos inmunológicos (drogas anti-CTLA4 o anti PD-1). Es importante reconocer aquellas drogas que generan hipotiroidismo por interacción en su tratamiento, ya sea disminuyendo la absorción o alterando el transporte y metabolismo de la levotiroxina. Sería recomendable evaluar la función tiroidea previa a la prescripción de medicamentos como amiodarona, litio o interferón, y a las nuevas terapias biológicas que muestran importante interacción sobre la función tiroidea y endocrina en general.

Palabras clave: tiroides, hipotiroidismo, fármacos

The thyroid axis is particularly prone to interactions with a wide variety of drugs and natural substances, the number of which increases every year. These substances affect every aspect of thyroid physiology and hormone pharmacology[1]. It is therefore important to recognize these interactions in order to avoid therapeutic failures, unnecessary therapies or false diagnoses[2]. These interactions lead to different forms of thyroid disorders (dysfunction, goiter, etc.), the most common of which, hypothyroidism[2], will be discussed below.

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The mechanisms responsible for drug-induced hypothyroidism can be summarized as follows[2]:

a) Inhibition of synthesis and/or release of thyroid hormones

b) Immune mechanisms

c) Drug-induced thyroiditis

d) Mixed: tyrosine kinase inhibitors

e) Inhibition of tyroid-stumulating hormone (TSH) synthesis

f) Interactions in the treatment of hypothyroidism

Many drugs can induce both primary and central hypothyroidism through different mechanisms. Table 1 displays a list of these drugs and mechanisms.

Drug-induced primary hypothyroidism

a) Inhibition of synthesis and/or release of thyroid hormones

TABLE 1.– *Drugs that cause hypothyroidism*

– Primary hypothyroidism
Inhibition of synthesis and/or release of thyroid hormones
Thionamides
Iodine and iodine-containing drugs (amiodarone, contrast agents, etc.)
Lithium
Minocycline and other tetracyclines
Others: Aminoglutethimide. Thalidomide. Tuberculostatic drugs (ethionamide).
Immune Mechanisms
Interferon-alpha
Other cytokines (IFN β, IL-2)
Other mechanisms
Drug-induced thyroiditis (see Table 5). Increase in DIII activity*
Tyrosine kinase inhibitors
– Secondary hypothyroidism
Inhibition of TSH synthesis
Bexarotene
Immune mechanisms
Anti-CTLA4
– Interactions in the treatment of hypothyroidism
Decrease in levothyroxine absorption
Alteration in transport and metabolism of thyroid hormones

** Type III deiodinase*

1. *Thionamides*

Their inhibitory effect on thyroid function has been known since 1943. Astwood suggested the use of thionamides to treat hyperthyroidism and named them antithyroid drugs[3]. Their main action is to interfere with thyroid peroxidase both in the oxidation and organification of iodide and in the iodotyrosine coupling process[4]. Since antithyroid drugs are used to treat hyperthyroidism, their pharmacological effects should not be considered undesirable.

2. *Iodine and iodine-containing drugs*

Iodine was discovered in 1811 by Bernard Courtois and its name comes from the Greek word "iodes", which means violet[5]. The main effects of iodine excess on the thyroid are[6, 7]:

- Decrease in iodide transport
- Decrease in iodide oxidation and organification (Wolff-Chaikoff effect)
- Rapid blockade of thyroid hormones release through inhibition of intrathyroidal lysosomal activity, preventing thyroglobulin hydrolysis
- Immunostimulation
- Decrease in thyroid vascularization

An excessive iodine intake increases the risk of hypothyroidism and thyroid autoimmunity[7]. The thyroid cell has several self-regulating functions protecting it from a sudden increase in iodide serum levels. In the presence of high concentrations, there is a decrease in iodide oxidation and thyroid hormone synthesis (Wolff-Chaikoff effect). This effect is usually transient in normal individuals, an "escape" phenomenon occurring in approximately two weeks. The efficiency of the sodium/iodide symporter decreases over a few weeks, thus restoring the intrathyroidal iodide pool and thyroid hormone synthesis toward normal[8].

In normal individuals, exposure to pharmacological doses of iodine normally produces a slight temporary decrease in thyroid hormone levels. In patients with lower thyroid reserve (autoimmune thyroiditis, goiter), the escape from the Wolff-Chaikoff effect is impaired, resulting in hypothyroidism[6].

The predisposing factors for Iodine-induced hypothyroidism are[8]:

- Autoimmune thyroiditis
- Post-treatment of hyperthyroidism
- Previous hemithyroidectomy for the treatment of nodular goiter
- A history of postpartum thyroiditis, subacute thyroiditis, drug-induced thyroiditis
- Thalassemia major (thyroid hemosiderosis)
- Chronic renal disease

In euthyroid patients (especially children and the elderly), acute exposure (computed tomography scan with contrast agent)[9] or prolonged exposure (topical or systemic) to iodine may result in hypothyroidism which is resolved by withdrawal. As iodine easily passes through the placenta, it can induce fetal goiter or hypothyroidism. Vaginal application of povidone-iodine during delivery, or topical use of disinfectants in newborns may also promote transient neonatal hypothyroidism[10].

Exposure to iodine-based compounds is also reflected in alterations of laboratory tests[11]:

- TSH increase
- Decrease in thyroid hormones levels
- Increase in the amount of urinary iodine excretion over 24 hours

Even the administration of kelp-based preparations may affect thyroid economy modifying the hormone profile[11].These alterations return to normal within 2-3 weeks following treatment withdrawal, with the exception of contrast agents and amiodarone (see below).

The main iodine-containing drugs are shown in Table 2.

TABLE 2.– *Iodine-containing drugs*

Group	Representative drug	Iodine amount per unit
Anti-arrhythmic drugs	Amiodarone	75 mg/tablet
Radiocontrast agents	Iopanoic acid	333 mg/tablet
	Ipodate sodium	308 mg/tablet
	Other IV* preparations	140-380 mg/ml
Expectorants	Iodinated glycerol	15 mg/tablet
Topical antiseptics	Povidone-iodine	10 mg/ml
Anti-amebiasis agents	Iodoquinol	134 mg/tablet
Iodides	Lugol's solution	6-8 mg/drop
	Potassium iodide	38 mg/drop
Anti-cellulite treatments and natural preparations	Cellasene	240 µg/capsule**
	Kelp and vitamin preparations	150 µg/tablet***
Ophthalmic solution	Idoxuridine	18 µg/drop****

**Intravenous **3 capsules/day ***1 to 3 tablets/day ****2 drops qid*

Iodinated contrast agents

They are used in a wide range of imaging studies, such as angiography, venography, pyelography, endoscopic retrograde cholangiopancreatography, myelography and computed tomography scan among others.

Hydrosoluble preparations used in diagnosis and angioplasty contain 30-60% of iodine. In general, 70-100 ml are used per study (which provides 30-35% of the halogen).

Around 20% of patients (without previous thyroid pathology) may develop thyroid dysfunction (hypo and hyperthyroidism) following administration of an iodinated contrast agent[9].

In patients undergoing contrast studies, it is advisable to wait for two months before administering radioiodine (diagnostic or therapeutic). It is advisable to rule out thyroid pathology before indicating contrast studies, especially in children, elderly patients and patients with renal insufficiency[9, 12].

Amiodarone

Amiodarone is a benzofuran derivative with high iodine content (39% of its molecular weight). There is a structural similarity between amiodarone, its main metabolite: desethylamiodarone (DEA), and the thyroid hormones (Figure 1), so the drug behaves as a partial agonist of these hormones developing agonist activity in tissues such as the pituitary gland and antagonist activity in the heart[13, 14].

Each 200 mg tablet of amiodarone contains around 75 mg of iodine, so a 200-600 mg/day dose releases 7-21 mg of inorganic iodine into the systemic circulation during its hepatic metabolism[14]. This represents a contribution 50-100 times higher than the recommended daily intake of iodine of 150-250 µg. Deposits of the drug will be found in the adipose tissue, the liver, the connective tissue, the heart and the skeletal muscle, and the thyroid gland itself. It has an elimination half-life of around 100 days[15]. Amiodarone clearance is reduced in obesity by 22% and in patients over 65 years of age by 46%[16]. Due to its extensive tissue accumulation, the drug's effect persists between months and years after withdrawal.

The effects of amiodarone on the thyroid axis are related to its iodine content (previously described) and to amiodarone itself (Table 3).

Successive deiodination is the main metabolic pathway of thyroid hormones, yielding active and inactive metabolites[17]. Initial T_4 deiodination can occur at the outer ring producing T_3 (3, 3´, 5 T_3), or at the inner ring forming reverse T_3 (3, 3´, 5´ T_3). Less than 20% of total T_3 is produced in the thyroid; the rest results from deiodination in peripheral tissues[17].

Deiodination of thyroid hormones is catalyzed by deiodinase isoenzymes (*DI, DII, DIII*)[17]. Amiodarone inhibits *DI* activity in peripheral tissues, which results in a 30% decrease in serum concentrations of T_3 and increases of 20-40% in T_4 levels and of 20% in reverse T_3. In turn, inhibition of *DII* activity at pituitary level is responsible for increased TSH serum levels[18].

Amiodarone also decreases intracellular T_4 transport and T_3 binding to its nuclear receptors.

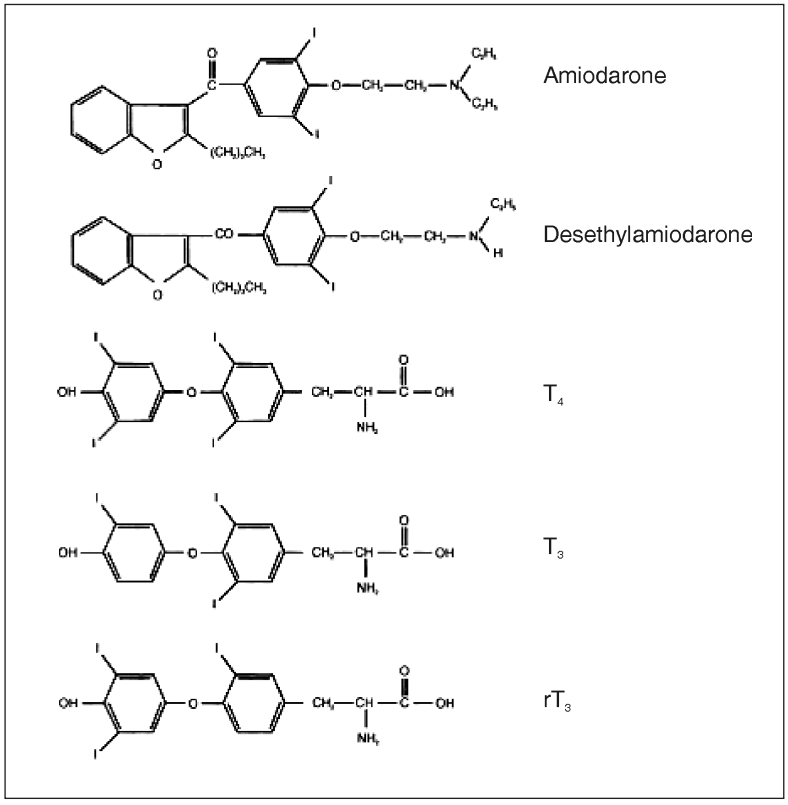

Fig. 1.– Chemical structure of amiodarone, desethylamiodarone, and thyroid hormones

TABLE 3.– *Effects of amiodarone on the thyroid*

Iodine-induced:
– Decrease in iodide transport
– Decrease in the synthesis of thyroid hormones (Wolff-Chaikoff effect)
– Rapid blockade of thyroid hormone release
– Blockade of131I uptake by isotope dilution
– Decrease of antithyroid drug activity
Amiodarone-induced:
– Inhibition of type I 5' deiodinase
– Inhibition of type II 5' deiodinase
– Decrease in intracellular T_4 transport
– Antagonist action on T_3 receptors
– Thyroid cytotoxicity

As a result of these actions, patients treated with amiodarone show alterations in thyroid hormones and TSH serum levels. These changes should be distinguished from a real dysfunction of the thyroid axis which may also occur during treatment[19]. Table 4 shows the laboratory alterations of the thyroid axis induced by amiodarone according to length of treatment.

Amiodarone-induced hypothyroidism (AIH)

Amiodarone-induced hypothyroidism usually appears within the first 6-18 months of treatment. It is more frequent among women, elderly patients, those with pre-existing autoimmunity and in areas with sufficient iodine intake. It can be observed in about 5-25% of treated patients[20], and it is often secondary to the presence of a smaller thyroid reserve, due to underlying autoimmune thyroiditis, treatment with ^{131}I, thyroid surgery, or the presence of predisposing chronic diseases, such as thalassemia major[21]. Clinical manifestations do not differ from those observed in primary hypothyroidism. Amiodarone-induced hypothyroidism, if sustained or severe, may induce ventricular arrhythmias[18]. Less commonly, it has been associated with acute renal insufficiency, which is reversible after treatment with levothyroxine and discontinuation of amiodarone[22]. It should be pointed out that amiodarone-induced hypothyroidism does not depend on the dosage of amiodarone administered. Amiodarone concentration and its cumulative doses do not differ between patients who remain euthyroid and those who develop hypothyroidism in the course of treatment with amiodarone[15]. Spontaneous remission of amiodarone-induced hypothyroidism does not occur if treatment with amiodarone is continued. In patients with

TABLE 4.– *Thyroid function tests in euthyroid subjects treated with amiodarone*

	3-6 – month therapy	Therapy > 6 months
T_4	High	High or normal
T_3	Low	Low or low normal
TSH	High (usually < 20 mUI/l)	Normal*
Reverse T_3	High	High
Urine iodine excretion	Increases ~ 50 times with a maintenance dose of 200 mg/day (normal values: 150 to 300 µg/day)	

**Periods of slightly increased or decreased TSH may alternate*

previously normal thyroid function, interruption of the drug promotes recovery within 2-4 months in 60% of the cases. In the remaining 40%, it may persist for 5-8 months more.

In patients with previous thyroid dysfunction, hypothyroidism will persist even after discontinuation of amiodarone, requiring chronic levothyroxine therapy[15].

In any of these scenarios, it is not necessary to interrupt amiodarone administration in the presence of hypothyroidism.

The decision about whether to treat amiodarone-induced hypothyroidism or not depends on the degree of dysfunction, the patient's age and, in particular, on the underlying cardiac condition[15, 18]. In the presence of mild subclinical hypothyroidism (TSH < 10 uUI/ml), control without treatment may be sufficient. Low-dose levothyroxine (LT4) therapy can be initiated, starting with 25 mcg/day if treatment is required. Serum TSH levels should be assessed after 4-6 weeks, and the LT4 dose increased slowly every 4 or more weeks according to tolerance and cardiovascular controls, maintaining higher TSH levels than in other cases of hypothyroidism[13].

At the other end of the amiodarone-induced hypothyroidism spectrum is myxedema coma. This condition is extremely severe and reinforces the concept of regular examinations of thyroid function in patients treated with amiodarone[23]. Amiodarone may also induce destructive thyroiditis due to direct cytotoxic damage of thyroid follicular cells causing thyrotoxicosis. About 15% of the cases subsequently develop hypothyroidism[13].

In summary, monitoring of thyroid function is necessary in every patient that may need amiodarone treatment and should conveniently be performed before the beginning of treatment, requiring subsequent assessments after the first month, the third month, and every six months thereafter[13].

3. *Lithium*

Lithium carbonate (Li_2CO_3) is an alkali cation of widespread use in neuropsychiatry. It is estimated that around 1 in 200 people receives lithium to treat bipolar disorder[24]. Lithium is concentrated in the thyroid in a ratio 3-4 times higher than in plasma[24]. It increases intrathyroidal iodine content, inhibits iodotyrosine coupling and blocks the release of thyroid hormones[24]. *In vitro*, it decreases colloid droplet formation within thyroid cells, a reflection of lower colloid pinocytosis from the follicular lumen. The inhibition of thyroid hormone secretion promotes a higher TSH secretion, which results in an increased thyroid volume. Additionally, it might induce signaling alterations in IGF-1, in other tyrosine kinases and in Wnt/beta-catenin signaling, favoring cell proliferation and the resulting goitrogenesis[25]. Cross-sectional studies have revealed the presence of diffuse goiter in 40-50% of patients treated with lithium within the first 5-10 years[26].

The prevalence of lithium-induced hypothyroidism varies between 6 and 52% according to several series, and it is usually subclinical[26], though severe hypothyroidism and also myxedema coma has been reported[27]. Lithium-induced hypothyroidism is more frequent among women and in the first two years of treatment[24]. In many cases, there is an underlying component of autoimmune thyroiditis[26, 28]. Treatment of hypothyroidism does not require withdrawal of lithium and is carried out with levothyroxine in usual doses. Before starting treatment with lithium, a thyroid test should be obtained and it should be repeated every 6-12 months[24].

4. *Minocycline*

It is an antibiotic of the tetracycline group used to treat acne vulgaris. Benitz et al. initially described minocycline-induced black thyroid in 1967[29]. Over the following decades, about 125 cases were reported in the literature[30]. Even though the black pigmentation of the thyroid has been considered pathognomonic of chronic minocycline intake, other tetracyclines such as doxycycline may induce it in just 12-day long treatments[31]. This pigmentation may also affect other tissues such as skin, sclera, bone, teeth, gingiva and nails[32]. The insoluble black pigment results

from minocycline oxidation by thyroid peroxidase[30]. Minocycline may also inhibit thyroid function and may have goitrogenic effects[33], which might be due to a blocking of the peroxidase activity on the coupling reaction[32].

b) Immune mechanisms

The first descriptions associating thyroid dysfunction with interferon-alpha therapy (IFN alpha) date back to 1986[34]. Its use has noticeably increased over the last few years in the treatment of diverse neoplastic and infectious entities such as leukemia, condyloma acuminatum, Kaposi's sarcoma and, particularly, hepatitis B and C[35]. IFN-alpha activates a series of intracellular signals including JAK-STAT, CRK, IRS, and MAP-kinase pathways, stimulating transcription of the specific proteins responsible for mediating their antitumor immunomodulating effects[34]. Thus, the expression of class I proteins from the major histocompatibility complex increases and this may lead to higher exposure of autoantigens promoting thyroid damage. The mechanisms through which IFN-alpha induces thyroid dysfunction are still not clear. The recruitment of immune cells (natural killer cells) capable of damaging the thyroid or even a direct cytotoxic effect has been suggested[36]. One of the most common side effects of IFN-alpha is thyroiditis, described in 20-40% of cases, of which 5-20% develop thyroid dysfunction[34, 37]. Such complications may arise at any stage of treatment, even 6 months after discontinuation and are more common in female patients[34]. Persistent hypothyroidism is frequent after discontinuation of IFN-alpha[38]. It should be highlighted that both the presence of thyroid autoimmunity prior to treatment as well as an underlying genetic predisposition enhance the risk of developing IFN-alpha-induced autoimmune thyroiditis[36, 38].

Considering the frequency of thyroid complications in patients treated with IFN-alpha, it would be advisable to request an antithyroid antibody test before starting treatment. Patients with hepatitis C are more prone to develop autoimmune and non-autoimmune thyroiditis induced by IFN-alpha since there might be a molecular mimicry phenomenon between the virus and thyroid antigens[39].

Since the symptoms of hypothyroidism, such as fatigue and weight gain, may be attributed to hepatitis C or to IFN-alpha treatment, its diagnosis is usually delayed[34]. Treatment of INF-alpha-induced hypothyroidism should be regularly monitored (every 2-3 months) as dysfunction may be progressive requiring adjustments of the replacement dose. If treatment with INF-alpha is interrupted, it is necessary to evaluate the possibility of decreasing or even discontinuing hormone therapy[34].

Other cytokines that may induce or exacerbate autoimmune thyroiditis are interferon beta[40] and interleukin-2[41].

c) Drug-induced thyroiditis

Drug-induced thyroiditis can be the result of several mechanisms, the most common being an inflammatory/destructive process induced by drugs. These alterations start with an initial thyrotoxicosis phase due to the massive release of thyroid hormones into the circulation. After this, hypothyroidism is observed, which can be transient if full restoration of the thyroid tissue occurs[42], or permanent. In other cases, thyroiditis is caused by the induction of immune mechanisms or by the blocking of the vascular endothelial growth factor receptor (VEGFR), as occurs with tyrosine kinase inhibitors[42]. The mechanisms of drug-induced thyroiditis may be summarized as follows:

- Cytotoxic
- Immune dysregulation
- Ischemic, by blocking the vascular endothelial growth factor receptor

Table 5 provides a list of the drugs that may induce thyroiditis.

d) Mixed: tyrosine kinase inhibitors

Tyrosine kinase inhibitors may induce hypothyroidism by different or mixed mechanisms over thyroid economy[42].

The first description of tyrosine kinase inhibitor-induced hypothyroidism dates back to 2005, in patients with medullary thyroid cancer treated with imatinib[43]. Other tyrosine kinase inhibitors responsible for inducing hypothyroidism, as seen in several published cases, are sunitinib, sorafenib, cabozantinib, vandetanib, lenvatinib, etc. Although the use of these drugs initially focused on the treatment of gastrointestinal stromal tumors and re-

TABLE 5.– *Drugs-induced thyroiditis*

–	Cytotoxic
	Amiodarone
	Lithium
	Hebrix® (ioxaglate sodium –ioxaglate meglumine)
	Minocycline
–	Immune dysregulation
	Lithium
	Tyrosine kinase inhibitors
	IFN α, IFN β, IL-2 / Denileukin diftitox / Etanercept / Lenalidomide
	Monoclonal antibodies: Anti-TNF α (Infliximab) / Anti PD1 (Pembrolizumab, Nivolumab) / Anti-CTLA-4 (Ipilimumab)
–	Ischemic
	Tyrosine kinase inhibitors (blockade of VEGFR)

nal carcinoma, some of them are currently approved for the treatment of metastatic differentiated thyroid cancer (lenvatinib, sorafenib) and medullary thyroid cancer (vandetanib and cabozantinib). Currently, the incidence of tyrosine kinase inhibitor-induced hypothyroidism is estimated to be present in more than 50% of cases[44].

Tyrosine kinase inhibitors promote hypothyroidism through several mechanisms, the most relevant of which are:

- Ischemic thyroiditis due to a marked capillary regression caused by blocking the vascular endothelial growth factor[45].

- Higher thyroid hormone metabolism due to hepatic microsomal and *DIII* induction[4].

Further effects of tyrosine kinase inhibitors on the thyroid include: inhibition of iodine organification, inhibition of peroxidase[46], blocking of iodine uptake, thyroid autoimmunity[47] and alteration of the intestinal absorption and of the enterohepatic reabsorption of levothyroxine[42]. Around 30-35% of patients treated with tyrosine kinase inhibitors present transient increase of TSH levels which requires no treatment[48]. Consequently, it is advisable to perform an initial thyroid examination, followed by assessments every 4 weeks during 4 months, and finally every 2-3 months during treatment with tyrosine kinase inhibitors [49].

Mechanisms of secondary/central drug-induced hypothyroidism

a) Inhibition of TSH synthesis

1. *Bexarotene*

Bexarotene is a synthetic compound that represents a new subgroup of retinoids that activate retinoid X receptors (RXRs), which can therefore be defined as a rexinoid agent. It is used in the treatment of cutaneous T-cell lymphoma and induces central hypothyroidism due to TSH suppression in 90% of cases[50]. Bexarotene, like T_3 and 9-cis-retinoic acid, produces about 50% *in vitro* suppression of the gene promoter of TSH beta-subunit. It also stimulates the peripheral metabolism of thyroid hormones by induction of glucuronyl transferases and sulfotransferases[51]. Thus, patients with bexarotene-induced hypothyroidism usually require higher hormone replacement doses (up to two times higher)[52]. Hypothyroidism appears a few days after treatment is started and all patients recover thyroid axis function after discontinuation. This effect is not observed with 13-cis-retinoic acid (isotretinoin), which is used for severe acne.

2. *Somatostatin analogues*

With respect to thyroid axis, somatostatin analogues have demonstrated therapeutic effectiveness in patients with the syndrome of pituitary resistance to thyroid hormones and with thyrotropinomas[53]. Administration of somatostatin to healthy volunteers decreases both TSH pulse frequency and amplitude[54]. Colao et al. stated that prolonged use of somatostatin analogues reduces TSH and its response to stimulus with thyrotropin-releasing hormone without affecting serum levels of thyroid hormone[55]. In a review of somatostatin analogues in acromegaly, an incidence of 2% of central hypothyroidism is described[56]. However, it is estimated that, although somatostatin analogues suppress TSH through direct action on thyrotropes, these effects are mainly temporary and generally do not promote the appearance of central hypothyroidism[57].

3. *Glucocorticoids and dopamine*

The influence of glucocorticoids on TSH secretion has been long acknowledged[58]. At physiological levels, hydrocortisone plays an important role in the diurnal variation of TSH, showing lower levels in the morning and higher levels at night[54]. This explains why TSH levels are high in patients with untreated adrenal insufficiency. Glucocorticoids in high doses suppress TSH in both normal and in hypothyroid subjects. A prolonged administration of glucocorticoids in high doses does not usually cause central hypothyroidism. Recent publications suggest the presence of central hypothyroidism in patients with corticotroph microadenomas produced by the suppression of the hypothalamic-pituitary-thyroid axis induced by an excess of cortisol[58].

Dopamine and its agonists, such as bromocriptine, suppress TSH secretion by activating its D_2 receptors[57]. Although the administration of dopamine or its derivatives dobutamine and dopexamine may cause difficulty in the interpretation of TSH serum levels, it does not induce central hypothyroidism. If ultrasensitive methods detecting TSH levels within the range of 0.01 mUI/ml are used, TSH values during treatment with these drugs are usually between 0.08 and 0.4 μUI/ml. These values are clearly different from those commonly observed in hyperthyroidism (TSH lower than 0.01 μUI/ml)[59].

b) Immune mechanisms

1. *Anti-Cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibodies*

Monoclonal anti-CTLA-4 antibodies are used in the treatment of several neoplasias, such as metastatic renal carcinoma and melanoma among others. The administration of ipilimumab or tremelimumab may induce the development of acute lymphocytic hypophysitis with panhypopituitarism; central hypothyroidism being the most frequent deficiency (90% of cases)[60]. Hypophysitis is observed in 7-13% of the patients treated with ipilimumab, who present with headache as the most frequent symptom[61]. It is more common in male patients with an average age of 60 and usually appears after 2 -4 months of treatment, typically after the

third cycle[60]. The differential diagnosis is with metastatic melanoma and other pituitary tumors. A nuclear magnetic resonance can help diagnose hypophysitis by revealing pituitary enlargement with an increased longitudinal diameter, thickening of the stalk, suprasellar convexity and a hyperintense heterogeneous signal[62]. Ipilimumab-induced hypophysitis is generally characterized by the absence of diabetes insipidus unlike postpartum or gestational autoimmune hypophysitis[62]. Ipilimumab can also affect the thyroid function (though less commonly) and has been associated with primary adrenal insufficiency as well[63].

2. *Anti-Programmed cell death-1 receptor (anti-PD-1) antibodies*

Hypophysitis induced by anti-PD-1 such as pembrolizumab and nivolumab is far more unusual, with few cases described[64]. On the other hand, the incidence of thyroid disorders induced by anti-PD-1 particularly silent thyroiditis is more common and occurs in 5-10% of patients[64].

Interactions in the treatment of hypothyroidism

Some drugs may reduce the intestinal absorption of levothyroxine by altering its transport and/or metabolism.

Drugs that decrease levothyroxine absorption

The gastrointestinal tract is of great importance in thyroid physiology, since conjugated iodothyronines are excreted in bile and are partially unconjugated in the intestine by bacterial enzymes, liberating a small amount of free hormones which are absorbed into portal circulation[65]. Less than 10% of the daily production of thyroid hormones is excreted in feces. Approximately 62-82% of orally administered levothyroxine is absorbed within the first three hours after intake, mainly in the jejunum and the ileum[66]. This absorption is higher when the drug is administered on an empty stomach, which shows the importance of gastric acidity in this process[67]. In hypothyroid patients receiving levothyroxine treatment, a wide range of drugs and dietary substances alter its absorption, preventing an adequate metabolic control[68].

Colestyramine, colestipol and colesevelam are bile acid binding resins used in hyperlipidemia which significantly inhibit absorption of thyroid hormones[69]. Because of its potent action, colestyramine is used in the treatment of exogenous hyperthyroidism and it is sometimes recommended, combined with methimazole, for a faster control of hyperthyroidism in Graves' disease[70]. Other drugs that can alter intestinal absorption of levothyroxine are sucralfate[71], aluminum hydroxide[72], proton-pump inhibitors[73], iron salts[74], calcium carbonate[75], and laxatives and antacids containing magnesium[76].

A reduced absorption of levothyroxine has been described when administered concomitantly with sodium sulfate polyestyrene (an ion-exchange resin used in hyperkalemia), sevelamer and lanthanum carbonate (phosphate binders), chromium[77], raloxifene[78], orlistat[66] and tyrosine kinase inhibitors[42].

The interaction of some dietary substances with thyroid hormone has become increasingly relevant due to the high consumption of bran and fiber for breakfast. Bran significantly inhibits intestinal absorption of levothyroxine[79], which makes it convenient to separate bran intake from hormone intake by a few hours. Soy-containing nutritional preparations also affect intestinal absorption of thyroid hormones[80]. A reduced absorption of levothyroxine has been described when consumed concomitantly with herbal remedies[81], prunes[81] and espresso coffee[82].

In all the above cases, interactions can be avoided if the administration of the hormone is separated from the intake of the above-mentioned drugs and foods by 4-6 hours[66]. Finally, it is worth pointing out that vitamin C may increase absorption of levothyroxine, therefore, in special cases such as gastritis, the concomitant intake of both may be convenient[83].

Drugs that alter levothyroxine transport and metabolism

More than 99% of thyroid hormones circulate bound to transport proteins: thyroxine-binding globulin, transthyretin (originally called 'thyroxine-binding prealbumin') and albumin[84]. Thyroxine-binding globulin transports about 70–75% of circulating T_4 and the rest is bound to transthyretin and/or albumin, while the circulating free form is lower than 0.001%[85]. Thus, thyroxine-binding globulin constitutes the main transport protein and the one most frequently affected by drugs[86], being able to modify total serum concentrations of thyroid hormones without compromising the patient's euthyroid state, since the free fractions are not modified[85].

Estrogens increase hepatic synthesis of thyroxine-binding globulin as well as its glycosylation, delaying its clearance and increasing its serum concentration[86]. This increase is dose-dependent and total T_4 levels rise by 20-35%[84]. On occasion, it could be necessary to increase the thyroid replacement dose in hypothyroid postmenopausal women undergoing estrogen therapy[87]. The same can be observed about the administration of oral contraceptives. These changes are usually seen within the first six weeks after starting estrogen therapy and the maximum effect is reached by week 12[87]. Evaluating the thyroid function 6-8 weeks after the start of oral estrogen therapy is recom-

mended in order to adjust the levothyroxine dose. These changes are not observed in the case of transdermal estrogen therapy, due to the absence of the first hepatic stage. In short, in hypothyroid women who might require estrogen replacement therapy, transdermal delivery would be more advisable.

The interruption of estrogen therapy or the drop in estrogen levels during menopause produces the opposite effect in hypothyroid women receiving levothyroxine, thus requiring a decrease in the dose of thyroid hormone[85]. In hypothyroid patients who become pregnant, estrogens induce a higher levothyroxine requirement of about 40-50% above the pre-pregnancy replacement dose[88]. Due to their estrogenic agonist effect at hepatic level, tamoxifen and other selective estrogen receptor modulators modify the thyroid profile of hypothyroid women who may therefore, also require an adjustment of the levothyroxine dosage[89].

A wide variety of drugs affect thyroid hormones metabolism, especially through intrahepatic deiodination, increased activity of CYP3A4, and conjugation with sulfate and glucoronic acid (enzyme induction). The main drugs involved are phenobarbital, carbamazepine, rifampicin and phenytoin[90-92]. In healthy subjects, the hypothalamic-pituitary-thyroid axis compensates for this situation increasing the production and secretion of thyroid hormones, and T_4, T_3 and TSH remain normal. In hypothyroid patients, this compensatory mechanism fails and it may be necessary to increase levothyroxine replacement doses.

In conclusion, the aim of this review is to draw attention to some major aspects of clinical practice that may go unnoticed. For example, when drugs such as amiodarone, lithium or immunomodulators are to be prescribed, the thyroid function should be previously assessed and regularly monitored thereafter.

It is also necessary to bear in mind that the intake of levothyroxine should be separated from that of drugs or foods that may impair its absorption. Similarly, those drugs that interfere with the transport and metabolism of the exogenous hormone should be taken into account and the corresponding dose adjustments should be made in hypothyroid patients.

Further consideration should be given to those drugs that alter thyroid function tests leading to false diagnoses and unnecessary therapies.

Finally, the new biological immunomodulating and antineoplastic therapies enlarge the battery of drugs which substantially interact with thyroid function and endocrine activity in general.

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NIVEL, A

"Usted enfoca el problema ingreso a nivel del estudiantado". "Enfoquemos el análisis a nivel grupal".

Adolfo Bioy Casares (1914-1999)

Breve diccionario del argentino exquisito. Buenos Aires: Emecé, 1978, p 103