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Therapeutic Drugs Causing Thyroid Disorders

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Abstract: Thyroid function can be influenced by drugs in many ways. Drugs like Lithium, Iodinated drugs, Interferon alpha, Dexamethasone, Salicylates, Androgens, Anabolic steroids, Rifampicin and many others alter Thyroid activity by varying mechanisms. In this review we have tried to include number of drugs leading to thyroid disorder. Knowledge about this is required as physicians dealing with the patients and patients who are taking these medications should have deep knowledge about the possible causes and management of these disorders.

Keywords: Thyroid disorders; amiodarone; lithium; interferon alpha; Improved diagnostic tools

Introduction

Many drugs and medications can affect thyroid function [1]. Due to number of newer molecules increasing day by day, it is very essential that physicians should recognize the drugs related thyroid disorders so that medical treatments which are dangerous could be prevented and also the inappropriate cost of the therapy could be reduced [2,3].

Pharmacological agents can affect thyroid hormone function at different levels:

i. Serum concentration of thyroid hormone may change by these agents either by varying level of binding proteins or by competing for their hormone binding sites.
ii. Synthesis or secretion pertaining to thyroid hormones may be affected.
iii. They may alter thyroid hormone metabolism and cellular uptake.
iv. By interfering hormone action at the targeted tissue level [3].

1. Amiodarone an iodinated drug

Drugs in this group included are Iodinated Radiographic Contrast agents (I^{131}) and antiarrhythmic drug Amiodarone. Since 1949, I^{131} is used for treating both benign and malignant thyroid disorders [4]. I^{131} therapy causes thyroid eye disease and also in patients suffering from Grave's disease may lead to hypothyroidism [5]. There can be intensive hyperthyroid symptoms due to radiation thyroiditis and the most disturbing and potentially bothersome is potential deterioration of thyroid associated opthalmopathy (TAO) [4]. The thyroid function is affected generally by the large iodine content of iodinated agents [6].

Amiodarone is classified as class III antiarrhythmic drug which is used in the treatment of recurring severe ventricular arrhythmias, paroxysmal atrial tachycardia, atrial fibrillation and maintenance of sinus rhythm after cardio version of atrial fibrillation [7]. Each molecule of amiodarone consists of 37.2% of iodine by mass and thus it is extremely iodinated [6]. If a 200 mg tablet is considered then about 75mg of iodine is present in it which is estimated to release 10% of iodine as free iodide daily [7].

Amiodarone usage may lead to hypothyroidism and thyrotoxicosis [8]. The relative occurrence of amiodarone induced thyrotoxicosis (AIT) and hypothyroidism (AIH) depends on iodine intake and any principle thyroid disorder. Areas where there is ample amount of iodine intake AIH is found to 10 times more common than AIT whereas if iodine consumption is not sufficient AIT is twice times more common than AIH in such areas [9]. Amiodarone induced hypothyroidism (AIH) is chiefly found in patients suffering with Hashimoto's thyroiditis [10]. The management of AIH is relatively simple and involves amiodarone withdrawal or thyroxine substitution [11].

1.1 There are two major types of AITs:

a. Type I: It is found in patients with latent or already existing thyroid ailments (such as nodular goiter, diffuse goiter, or Graves disease) and is usually found more in areas where there is low iodine intake. There is extreme, uninhibited synthesis of thyroid hormone by separately functioning thyroid tissue in response to iodine also known as (jodbasedow phenomenon).

b. Type II: It is found in patients who had earlier normal thyroid glands and is affected by destructive inflammatory thyroiditis, brought out by amiodarone or its iodine content. Various cytotoxic effects are

produced by the drug on thyroid follicles which generates inflammation via various mechanisms. Thus preformed thyroid hormones are released due to follicular disruption [12].

Therapy for the management of AIT is a challenge. Initial treatment involves the decision to continue or discontinue drug depending on the patient's cardiac health [13].

Type I AIT patients generally respond to thionamides (eg, carbimazole or methimazole 40–60 mg/day, or propylthiouracil 100–150 mg qid) and potassium perchlorate (250 mg 6 hourly). Type II AIT patients may generally require treatment with corticosteroids (eg, prednisone 40–60 mg/day) [11]. The other iodine containing organic compounds which are used for therapy and get somewhat deiodinated in vivo and thus affect thyroid function includes Saturated Solution Potassium iodine (amount of iodine - 38 mg/drop; Lugol's Iodine(amount of iodine - 6.3 mg/drop); Amiodarone (amount of iodine - 75mg/tablet); Iodoquinol(amount of iodine - 104 mg/tablet); Povidone Iodine (amount of iodine – 10 mg/ml); Theophylline elixir (amount of iodine - 6.6 mg/ ml); Iopanoic acid (amount of iodine - 333mg/tablet) etc [14].

2. Lithium

Lithium has been used as the most effective treatment for bipolar disorders which is protective against both depression and mania and decreases suicidal risk and short range mortality [15]. Lithium exerts many actions on thyroid functioning causing hypothyroidism and goitre [16]. Thyroid gland concentrates Lithium and shows the following adverse effects on thyroid function:

a. Iodine uptake is inhibited.
b. Coupling of iodotyrosine is inhibited.
c. Thyroglobulin structure is modified.
d. Thyroxin secretion is also inhibited [15].

Levothyroxine is the effective treatment considered for this, but lithium therapy should not be stopped. Lithium is also reported to cause hyperthyroidism in few patients due to thyroiditis or rarely Graves' disease [16]. Though Lithium related thyrotoxicosis is not very common but it does occurs if drug is used for a long term [17]. Lithium carbonate can also induce subclinical or overt hypothyroidism, chiefly in patients suffering with autoimmune thyroiditis. In subclinical hypothyroidism an increased level of serum TSH and thyroid hormone levels is observed at the lower limit but within the reference range [18]. It is still a controversy whether Lithium can induce thyroid autoimmunity [19].

3. Interferon alpha

Hepatitis C is one of the major causes of chronic liver infection and cirrhosis globally [20]. Alpha-interferon is used for the treatment of Hepatitis C Virus infection but due to its immunomodulatory properties it may cause autoimmune thyroiditis [21]. About 2–19% of IFN-α-treated patients are affected by this. In few cases Thyroiditis along with thyroid disfunction as hypothyroidism and thyrotoxicosis has been found. Silent thyroiditis is frequently observed whereas IFN-α-induced Graves' disease is not so common [22]. On the basis of epidemiological characteristics interferon induced thyroiditis (IIT) can be grouped into autoimmune IIT and non-autoimmune IIT. Autoimmune IIT can be noticed as Graves' disease (GD), Hashimoto's thyroiditis (HT), or the production of thyroid autoantibodies (TAb's) with no clinical disease, whereas non-autoimmune IIT exist as destructive thyroiditis, or non-autoimmune hypothyroidism [23].

3.1 The probable mechanism for IIT may be:

a. Upregulation of MHC class I antigen expression by interferon which encourages autoantibody formation.
b. Interferon treatment hastens human thyroiditis by encouraging Th1 switching.
c. Direct action of IFN on thyroid.

Though, further research is required in this respect [24]. The disease should be detected as early as possible so that complications lie cardiac arrhythmias could be avoided [25].

3.2 Treatment of IIT involves:

a. In Thyrotoxicosis cases: Mostly it occurs due to destructive thyroiditis (DT) or by Graves' disease (GD). DT patients could be treated with beta-blocker with follow up for the hypothyroidism development. IFN α therapy can be continued in many cases with consultation from physician. In IIT cases manifesting as grave's disease usually thyroid ablation with radioactive iodine or surgery is found to be appropriate. Antithyroid medicines are not recommended as it can deteriorate liver dysfunction.
b. Hypothyroidism cases: Treatment involves thyroid hormone replacement and there is no need to stop IFNα therapy. Observation is required for any progress in disease which may lead to increase in T4 requirements [23].

4. Dexamethasone

Dexamethasone is an effective glucocorticoid class of steroidal drugs which acts as an anti-inflammatory and immunosuppressant [26]. If large doses of this is given for a long period of time it may reduce TSH secretion from anterior pituitary thereby decreasing thyroid hormone secretion [27]. A possible mechanism for this has been suggested related to the inhibitory actions of the steroid which depends on novel RNA/protein synthesis and involves a Lipocortin C1 dependent mechanism [28]. Also it has been found that due to the inhibitory action on 5 deiodination T3 concentrations may get reduced [29].

5. Drugs that induce hepatic p450 complex

Antiepileptic drugs e.g. Phenytoin that induces hepatic P450 complex, effects thyroid hormone metabolism causing decrease in thyroxin levels. It may be clinically noteworthy in patients suffering from hypothyroidism and which are on replacement therapy [30]. With carbamazepine less marked effects have been reported. It declines serum concentrations of total (TT_4) and free (FT_4) thyroxine in epileptic patients. In few studies, total triiodothyronine (TT_3) concentrations were found to be normal or with a mild decrease and TSH (Thyroid stimulating hormone) levels were either slightly decreased or showed no change [31].

According to a study, hypothyroidism developed in the euthyroid patients with Hashimoto's thyroiditis within two weeks but was normal, once Rifampicin was stopped. This concluded that Rifampicin which is an anti-tubercular drug also affects thyroid hormone levels [32]. Phenytoin and Rifampicin both increases the rate of metabolic clearance of T4 (Thyroxine). In order to compensate for these, T4 level increases in normal persons but an increased dose of T4 is required in hypothyroid patients [33].

6. Drugs which change the thyroxine binding globulin (tbg) concentration

About 0.02% of circulating T4 and 0.1% of circulating T3 are free in humans. Hence the serum total T4 and T3 are equal to the amount of bound T4 and T3 [34]. Anabolic steroids and androgens e.g. Norethandrolone and methandrostenolone and relatively increased dose of glucocorticosteroids reduces the serum TBG, possibly by hindering hepatic synthesis [35].

Estrogen increases serum T4-binding globulin (TBG) concentrations as there is reduced elimination of more heavily sialylated TBG secreted by the liver. Thus, the serum total T4 concentration increases whereas serum free T4 concentrations remain usual. Tamoxifen, a selective estrogen receptor modifier (SERM) which is used for treating breast cancer is reported to increase serum TBG concentrations [36].

7. Drugs that compete with t4 and t3 to their binding sites on serum transport proteins

Drugs e.g. Salicylates and furosemide are included in this category. Salicylates, if given in doses greater than 2.0 g per day interferes with T4 and T3 binding to TBG and transthyretin and also cause depletion in serum T4 and T3 concentrations. Similarly, Furosemide if given in large doses inhibits T4 binding to its carrier protein causing increase in serum free concentration and decrease in serum total T4 concentration [14].

8. Improved diagnostic tools

Much work has been done in this area to overcome difficulties related to interpretation of thyroid function techniques. Some of which are:

a. An ultra-sensitive heterogenous electrochemical enzyme immunoassay has been developed for thyroid stimulating hormone determination in human serum by transforming a commercially available two-site immunoenzymometric assay which is useful for assessing hyperthyroid patients where an accurate determination of TSH <0.1 mIU $I^{-1}$is required [37]
b. A fast, easy, reliable and cost effective Thyroid stimulating hormone immunoassay was developed using Eu(III) nanoparticle label [38].
c. Thyroid hormone responsive reporter gene assay has been developed which can detect T3 activity at 10^{-11}M [39].
d. Autoimmunity has been found to be the major cause of thyroid disorders leading to the progress in this field dealing with determination of thyroid autoantibodies – thyroid peroxidise antibodies (TPOAb), thyroglobulin antibodies (TgAb), and TSH receptor antibodies (TRAb).
e. Further now, thyroid hormone binding proteins, Thyroxine Binding globulin (TBG), Transthyretin (TTR)/ Prealbumin (TBPA) and Albumin, as well as for the pituitary thyroid stimulator, thyrotropin (thyroid stimulating hormone, TSH) and the thyroid hormone precursor protein, Thyroglobulin (Tg) levels can be measured [40].

9. Conclusion

Many situations affect thyroid functions in humans but from the above summarized pharmacological agents it can be concluded that how various drugs also alter thyroid homeostasis which is of a great concern. These interfere with normal thyroid function by different mechanisms and may pose difficulty in thyroid function interpretation. Many improved diagnostic tools have come up in these years to overcome these problems. Knowledge regarding this is very essential for physician as well as patients which are being treated by these medications.

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