

Amiodarone and thyroid dysfunction



Case report

- ▶ A sixty year-old man developed subclinical hyperthyroidism in the fourth month of amiodarone use, which was prescribed for ventricular tachycardia and electrical instability due to Chagas heart disease. There were no symptoms of thyroid dysfunction, no goiter. Serum TSH level was <0.01 mUI/ml, negative thyroperoxidase antibody (TPOAb) and normal serum values of FT4 (0.8-1.9 ng/dl). Iodine uptake (RAIU) in 24 hours was 1%. A reduction in the amiodarone dosage was performed and the following serum TSH was 0.25 mUI/ml. After twelve months of follow-up, serum TPOAb became positive, and patient developed thyrotoxicosis, with FT4=1.9 ng/dl and TSH=0.20 mUI/ml. Despite an initial prescription of 40 mg/ day of prednisone for 2 months, the patient still presented thyrotoxicosis (FT4= 1.9 ng/dl and TSH=0.069 mUI/ml). Propylthiouracil was added to the prescription and patient restored euthyroidism after 5 months (FT4=1.58 ng/dl), still in use of amiodarone. Afterwards, cardiologists were able to take out amiodarone and the patient maintained euthyroidism. After that, it was also possible to withdraw prednisone and propylthiouracil from prescription.

INTRODUCTION

- ▶ Amiodarone, a class III antiarrhythmic drug, has multiple effects on myocardial depolarization and repolarization that make it an extremely effective antiarrhythmic drug. However, amiodarone is associated with a number of side effects, including thyroid dysfunction (both hypo- and hyperthyroidism), which is due to amiodarone's high iodine content and its direct toxic effect on the thyroid.



PHARMACOLOGY

- ▶ Amiodarone contains two iodine atoms. It is estimated that amiodarone metabolism in the liver releases approximately 3 mg of inorganic iodine into the systemic circulation per 100 mg of amiodarone ingested. The average iodine content in a typical American diet is approximately 0.3 mg/day. Thus, 6 mg of iodine associated with a 200 mg dose of amiodarone markedly increases the daily iodine load.



PHARMACOLOGY

- Amiodarone is very lipophilic and is concentrated in adipose tissue, cardiac and skeletal muscle, and the thyroid. Elimination from the body occurs with a half-life of approximately 100 days. Amiodarone toxicity can therefore occur well after drug withdrawal.
- The effects of amiodarone on thyroid function can be divided into those effects that are intrinsic properties of the drug and those effects that are due to iodine.


Intrinsic drug effects

- ▶ Amiodarone inhibits outer ring 5'-monodeiodination of thyroxine (T4), thus decreasing triiodothyronine (T3) production; reverse T3 accumulates since it is not metabolized to T2.
- ▶ Amiodarone (and particularly the metabolite desethylamiodarone) blocks T3-receptor binding to nuclear receptors and decreases expression of some thyroid hormone-related genes.
- ▶ Amiodarone may have a direct toxic effect on thyroid follicular cells, which results in a destructive thyroiditis.



Effects due to iodine

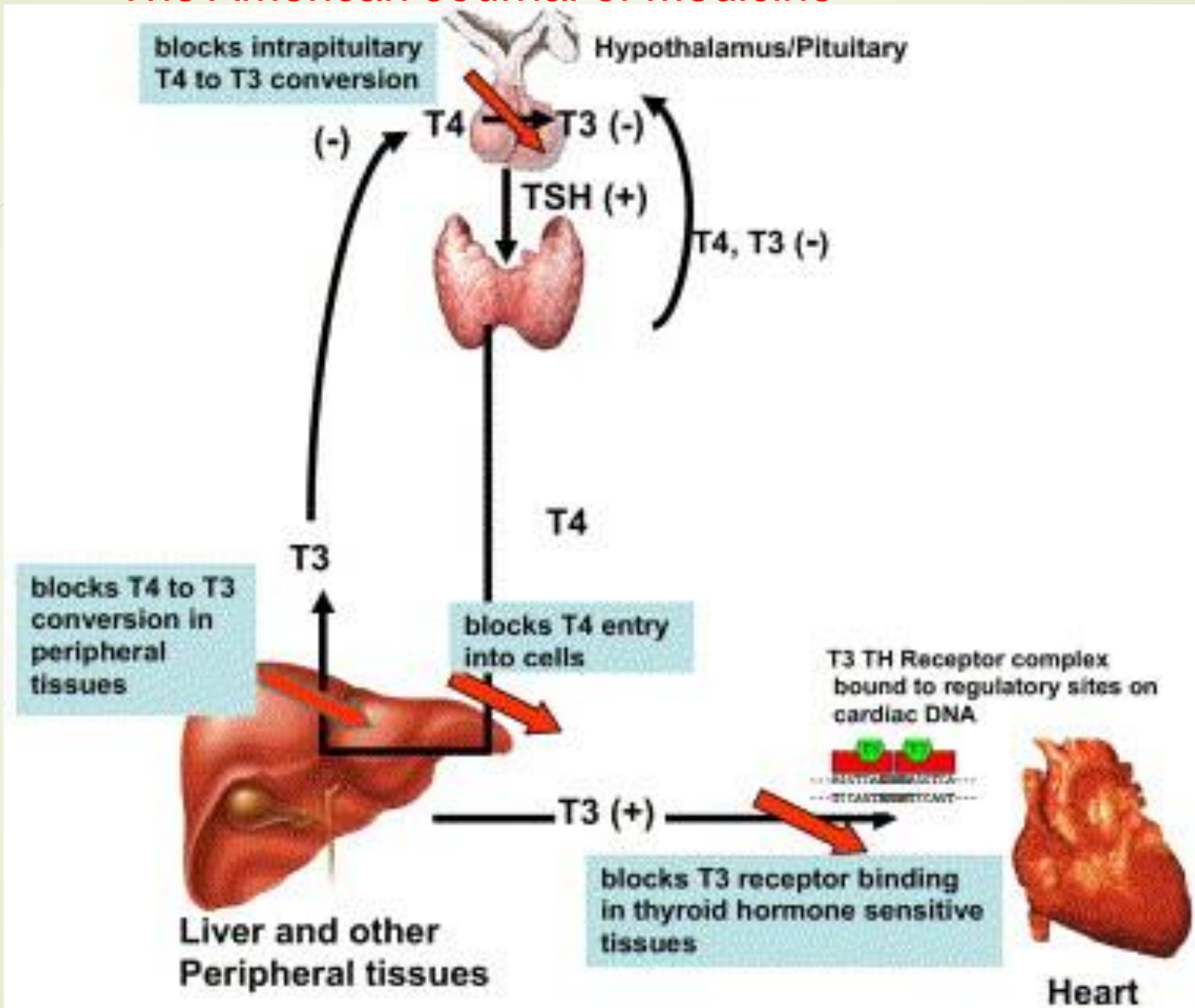
- ▶ Iodine is a substrate for thyroid hormone synthesis. It is actively transported into thyroid follicular cells and organified onto tyrosyl residues in thyroglobulin.
- ▶ The normal autoregulation of iodine prevents normal individuals from becoming hyperthyroid after exposure to an iodine load (eg, radiocontrast). When intrathyroidal iodine concentrations reach a critical high level, iodine transport and thyroid hormone synthesis are transiently inhibited until intrathyroidal iodine stores return to normal levels (the Wolff-Chaikoff effect).



Patients with underlying thyroid disease, however, have defects in autoregulation of iodine:

- ▶ Patients with autoimmune thyroid disease "fail to escape" from the Wolff-Chaikoff effect. The result is the development of goiter and hypothyroidism in Hashimoto's disease and amelioration of Graves' hyperthyroidism.
- ▶ Patients with areas of autonomous function within a nodular goiter do not autoregulate iodine and the addition of more substrate may result in excessive thyroid hormone synthesis and thyrotoxicosis.

The American Journal of Medicine

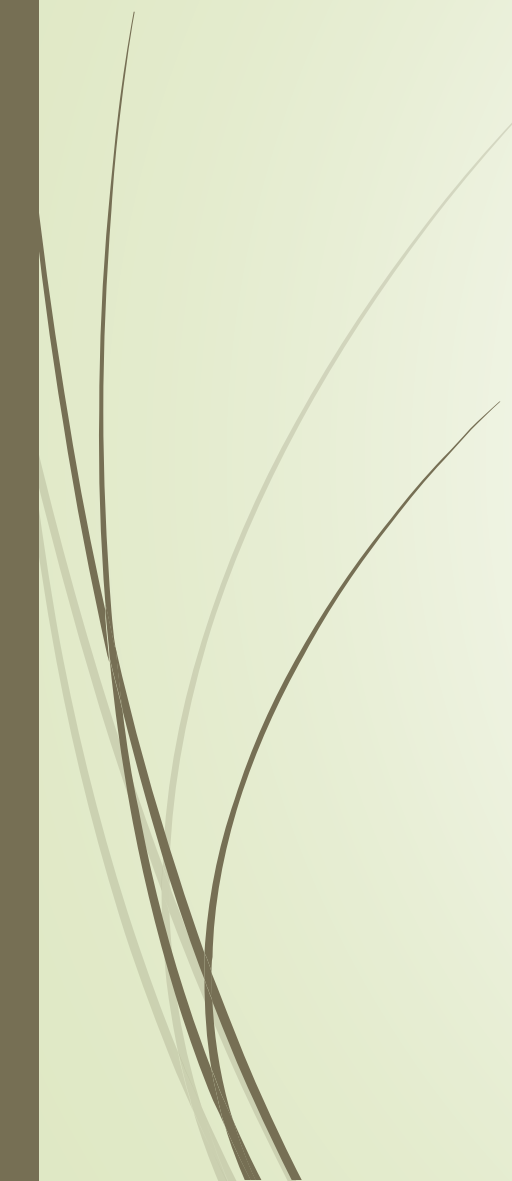


RISK OF THYROID DYSFUNCTION

- Both hypo- and hyperthyroidism are complications of amiodarone therapy. In a meta-analysis of four randomized trials involving 1465 euthyroid patients, the prevalence of clinical thyroid disease was higher in patients receiving amiodarone therapy (150 to 330 mg/day for a minimum of one year) when compared with placebo (3.7 versus 0.4 percent, respectively) . In other reviews and reports, the risk of amiodarone-induced thyroid dysfunction ranges from 2 to 30 percent, depending upon an individual's underlying thyroid status, dietary iodine intake, and whether cases of subclinical thyroid disorders (eg, slight rise in thyroid-stimulating hormone [TSH] without symptoms) are included.



Underlying thyroid function

- The clinical effects of amiodarone on thyroid function in any individual are dependent upon the underlying status of that individual's thyroid gland.
- 

Normal

In normal, euthyroid individuals receiving amiodarone, acute changes in thyroid function tests include:

- ▶ Serum T4 and free T4 concentrations rise by 20 to 40 percent during the first month of therapy.
- ▶ Serum T3 concentrations decrease by up to 30 percent within the first few weeks of therapy.
- ▶ Serum reverse T3 concentrations increase by 20 percent soon after the initiation of therapy.
- ▶ The serum TSH concentration usually rises slightly after the initiation of treatment and may exceed the upper limit of normal.

Normal

After three to six months of therapy, a steady state is reached in most patients who were euthyroid at baseline:

- ▶ Serum TSH concentration normalizes
- ▶ Serum total T4, free T4 and reverse T3 concentrations remain slightly elevated or in the upper normal range
- ▶ Serum T3 concentrations remain in the low normal range
- ▶ Amiodarone may also cause a destructive thyroiditis in patients without underlying thyroid disease

Abnormal

- ▶ Patients with underlying autoimmune thyroid disease are more likely to develop amiodarone-induced hypothyroidism, presumably due to failure to escape from the Wolff-Chaikoff effect.
- ▶ In patients with underlying multinodular goiter or latent Graves' disease, hyperthyroidism (increased synthesis of T4 and T3) may occur. The excess iodine from the amiodarone provides increased substrate, resulting in enhanced thyroid hormone production .

Differences Between Amiodarone-Induced Thyrotoxicosis Type 1 and Type 2

| | AIT Type 1 | AIT Type 2 |
|---------------------------------|-------------------|------------------------|
| Underlying thyroid abnormality | Yes | No |
| Onset after start amiodarone | Short (3 months) | Long (30 months) |
| Thyroid antibodies | Present in Graves | Usually absent |
| Color flow Doppler sonography | High vascularity | Low/absent vascularity |
| Thyroid radioiodine uptake | Low, normal, high | Suppressed |
| Preferred treatment | Antithyroid drugs | Oral prednisone |
| Amiodarone continuation | No | Possible |
| Spontaneous remission | No | Frequent |
| Subsequent hypothyroidism | No | Possible (17%) |
| Subsequent definitive treatment | Generally yes | No |

AIT, Amiodarone-induced thyrotoxicosis.

