Amiodarone is a potent class III anti-arrhythmic drug used in clinical practice for the prophylaxis and treatment of many cardiac rhythm disturbances, ranging from paroxysmal atrial fibrillation to life threatening ventricular tachyarrhythmias. Amiodarone often causes changes in thyroid function tests mainly related to the inhibition of 5'-deiodinase activity resulting in a decrease in the generation of T3 from T4 with a consequent increase in rT3 production and a decrease in its clearance. In a group of amiodarone-treated patients there is overt thyroid dysfunction, either amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH). AIT is primarily related to excess iodine-induced thyroid hormone synthesis in an abnormal thyroid gland (type I AIT) or to amiodarone-related destructive thyroiditis (type II AIT). The pathogenesis of AIH is related to a failure to escape from the acute Wolff-Chaikoff effect due to defects in thyroid hormonegenesis, or, in patients with positive thyroid autoantibody test, to concomitant Hashimoto’s thyroiditis. Both AIT and AIH may develop either in apparently normal thyroid glands or in glands with preexisting, clinically silent abnormalities. AIT is more common in iodine-deficient regions of the world, whereas AIH is usually seen in iodine-sufficient areas. In contrast to AIH, AIT is a difficult condition to diagnose and treat, and discontinuation of amiodarone is usually recommended. In this review we analyse, according to data from current literature, the alterations in thyroid laboratory tests seen in euthyroid patients under treatment with amiodarone and the epidemiology and treatment options available of amiodarone-induced thyroid dysfunctions (AIT and AIH).

Key words:
Amiodarone, Thyroid dysfunction, Thyrotoxicosis, Hypothyroidism.

Introduction

Amiodarone is a potent anti-arrhythmic drug used in clinical practice for the acute management of ventricular arrhythmias, paroxysmal supraventricular tachycardia, atrial fibrillation and flutter. As a category type-III anti-arrhythmic drug, its main mechanism of action is to block myocardial potassium channels, but it also possesses some beta-blocking properties.

Although highly effective in patients with arrhythmias, its use in clinical practice is associated with a wide array of adverse effects. With the cornea, the lungs, the liver, and the skin, the thyroid is one of the major organs affected.

The aim of this review is to analyse the diagnostic and therapeutic aspects of amiodarone-induced thyroid dysfunction according to recent literature.

All English language articles related to amiodarone and the thyroid were searched in MEDLINE from 1966 to 2006. The keywords included amiodarone and thyroid. The selection criteria included all prospective and retrospective studies, all clinical and basic reviews and basic science papers involving the pathophysiology of amiodarone.

Pharmacology of Amiodarone

Amiodarone is a benzofuranic derivative whose structural formula closely resembles that of human thyroid hormone T4. It contains approximately 37% iodine by weight. The maintenance daily dose of the drug in clinical practice ranges from 200 to 600 mg and, because approximately 10% of the molecule is deiodinated daily, approximately 7-21 mg iodide are made available each day, resulting in a marked increase in urinary iodide excretion.

If one considers that the optimal daily iodine intake is 150-200 µg, amiodarone treatment release 50- to 100-fold excess iodine daily.
Furthermore, amiodarone is distributed in several tissues, including adipose tissue, liver, lung, and, to a lesser extent, kidneys, heart, skeletal muscle, thyroid, and brain from which it is slowly released5.

The elimination half-lives averaged 52 ± 23.7 days for amiodarone and 61.2 ± 31.2 days for its metabolite desethylamiodarone (DEA) after cessation of long term amiodarone therapy5. Those considerations explain why, after amiodarone withdrawal, the drug and its metabolites remain available for long period. Amiodarone is metabolised through dealkylation, which leads to formation of DEA and approximately 66-75% of amiodarone is eliminated through bile and feces3.

**Amiodarone and the Thyroid**

Although the majority of the adverse effects of amiodarone on several organs are due to deposition of the drug in the parenchyma, its effects on the thyroid gland can be divided in two groups: intrinsic effects resulting from the inherent properties of the compound and iodine-induced effects due solely to the pharmacologic effects of a large iodine load (Table I).

Amiodarone acts on thyroid function through several mechanisms:

- Inhibits thyroid hormone entry into peripheral tissues6.
- Inhibition of type I 5’-deiodinase activity which removes an atom of iodine from the outer ring of T4 to generate T3 and from the outer ring of rT3 to produce 3,3’-diiodothyronine (T2). This inhibition may persist for several months after amiodarone withdrawal7,8.
- Inhibition of type II 5’-deiodinase which converts T4 to T3 in the pituitary. Indeed, after a loading dose of amiodarone by intravenous infusion, TSH is the first hormone to undergo significant variations, even during the first day of therapy9,10.
- Amiodarone may induce a hypothyroid-like condition at the tissue level partly related to a reduction in the number of catecholamine receptors and to a decrease in the effect of T3 on beta-adrenoreceptors11.
- Direct toxic effect of the drug on thyroidal cells12.
- Failure to escape from Wolff-Chaikoff effect13.
- In susceptible individuals amiodarone may precipitate or exacerbate preexisting organ-specific autoimmunity14.
- Unregulated hormone synthesis (Jod-Basedow effect)15.

**Effects of Amiodarone in Euthyroid Patients**

Although amiodarone-induced thyroid dysfunction represents an important clinical problem, the majority of patients receiving amiodarone remain euthyroid. Because the thyroid gland is exposed to an extraordinary load of iodine with amiodarone, important adjustments are made in thyroidal iodine handling and hormone metabolism in order to maintain normal function16, the reflection of which is seen in serum thyroid hormone levels. Those alterations in serum thyroid function tests can be divided into acute (less than 3 months) and chronic (more than 3 months) phases that follow amiodarone exposure during the pharmacologic therapy17 (Table II).

**Acute Effects**

*Serum T4 and T3*

The pharmacological concentrations of iodide associated with amiodarone treatment lead to a protective inhibition of thyroidal T4 and T3 syn-

<table>
<thead>
<tr>
<th>Table I. Effects of amiodarone on the thyroid gland.</th>
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<tr>
<td><strong>Intrinsic drug effect</strong></td>
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<tr>
<td>• Blockade of thyroid hormone entry into cells</td>
</tr>
<tr>
<td>• Inhibition of type I and type II 5’-deiodinase</td>
</tr>
<tr>
<td>• Decreased T3 binding to its receptor</td>
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<tr>
<td>• Thyroid cytotoxicity</td>
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</table>

thesis and release by thyroid tissue (called the Wolff-Chaikoff effect) within the first two weeks of treatment.

Amiodarone also inhibits the 5'-deiodination of T4 to T3 in the peripheral tissues, especially the liver and this inhibition persists during and for several months after the amiodarone treatment. The result is that serum T4 rises from pretreatment concentrations by an average of 40% after two months and remains at this higher level thereafter.

The absolute serum T4 in patients on moderate doses of amiodarone (200 mg/day) is usually towards the upper limit of the reference range (71-166 nmol/l). A group of clinically euthyroid patients will have serum T4 concentrations greater than 166 nmol/l and this increases with higher daily doses of amiodarone.

Serum T3 concentrations fall during amiodarone treatment, initially in part due to reduced thyroid synthesis and secretion, but principally because of reduced 5'-deiodination of T4 to T3 in peripheral tissues. T3 concentration usually remain within the reference range (1.3-3.0 nmol/l), but occasionally fall below 1.3 nmol/l.

Free T4 (FT4) and Free T3 (FT3)

As amiodarone has no effect on the serum concentration of thyroid hormone binding globulin, changes in FT4 and FT3 concentrations reflect those for total T4 and T3.

Serum Reverse T3 (rT3)

The reduction of peripheral metabolism leads to increased rT3 levels with amiodarone treatment.

Serum Thyroid Stimulating Hormone (TSH)

Serum TSH concentration rises transiently within a few days of starting amiodarone (Table III), but rarely reaches greater than 20 mU/l (reference range 0.35-4.3 mU/l). TSH then gradually return to baseline concentrations, or even slightly below, over the next one to three months.

The early rise in plasma TSH occurs largely in response to falling intrapituitary T3 concentrations consequent on reduced 5'-deiodination of T4 to T3, especially within the pituitary. Furthermore, desethylamiodarone (DEA), the principal metabolite of amiodarone, binds to intracellular T3 receptors and acts as a T3 antagonist.

Chronic Effects

After 3 months of amiodarone administering, a steady state is reached, with some hormonal changes persisting indefinitely. Total and free T4

Table II. Effects of amiodarone on thyroid function tests in euthyroid subjects.

<table>
<thead>
<tr>
<th>Thyroid Hormone</th>
<th>Acute effects (up to 3 months)</th>
<th>Chronic effects (&gt; 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total and free T4</td>
<td>↑ 50%</td>
<td>Remains ↑ 20-40% of baseline</td>
</tr>
<tr>
<td>Total and free T3</td>
<td>↓ 15-20%, remains in low-normal range</td>
<td>Remains ↓ 20%, remains in low-normal range</td>
</tr>
<tr>
<td>rT3</td>
<td>↑ &gt; 200%</td>
<td>Remains ↑ &gt; 150%</td>
</tr>
<tr>
<td>TSH</td>
<td>↑ 20-50%, transient, generally remains &lt; 20 mU/L</td>
<td>Normal</td>
</tr>
</tbody>
</table>


Table III. Reference ranges for serum thyroid hormones and TSH concentrations in euthyroid untreated subjects and in euthyroid patients receiving long-term amiodarone therapy.

<table>
<thead>
<tr>
<th>Test</th>
<th>Untreated patients</th>
<th>Patients on amiodarone treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free T4 (pmol/l)</td>
<td>11-20</td>
<td>12-24.7</td>
</tr>
<tr>
<td>Free T3 (pmol/l)</td>
<td>3-5.6</td>
<td>2.5-5.1</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>0.35-4.3</td>
<td>0.35-4.3</td>
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</table>

and rT3 remain at the upper end of normal or slightly elevated, and serum T3 levels remain in the low normal range. In contrast, serum TSH levels return to normal after 12 weeks of therapy.

The cause for TSH normalization is presumed to be an increase in the T4 production rate, possibly the result of increased intrathyroidal iodine stores and escape from the Wolff-Chaikoff effect that partially overcomes the blockade of T3 generation and raising serum T3 levels into the low-normal range.

Despite having high total and free T4 levels, amiodarone-treated patients are considered to be euthyroid because the serum concentration of T3, the major hormone responsible for end-organ effects, is in the low-normal range.

In summary, chronic amiodarone treatment for more than three months in clinically euthyroid patients is usually associated with high-normal or raised T4 and FT4, low-normal T3 and FT3, low-normal TSH, and high rT3 plasma concentrations (see Table II).

Using 99mTc thyroid scintigraphy the visualization of the gland appear very difficult and the 131I uptake remains constantly depressed in euthyroid patients treated with amiodarone.

Amiodarone-Induced Thyroid Dysfunction

Although the majority of patients given amiodarone remain euthyroid, some develop thyroid dysfunction like thyrotoxicosis and hypothyroidism.

Amiodarone-induced thyrotoxicosis (AIT) appears to occur more frequently in geographical areas with low iodine intake, whereas amiodarone-induced hypothyroidism (AIH) is more frequent in iodine-sufficient areas.

In general, the various published studies reported in overall incidence of AIT ranging from 1% to 23% and of AIH ranging from 1% to 32%. Significant risk factors for the occurrence of amiodarone-associated thyroid dysfunction are recognized. Those risk factors are female sex, complex cyanotic heart disease, previous Fontan-type surgery, and a dose of amiodarone > 200 mg/day.

Amiodarone-Induced Thyrotoxicosis (AIT)

AIT may develop early or after many years of amiodarone treatment and the average length of treatment before the occurrence of AIT is about 3 years. That fact may be partially due to tissue storage of the drug and its metabolites and to their slow release in blood flow so that the effect of amiodarone can persist for a long period of time.

A relative predominance of AIT among men, with a M:F ratio of 3:1, has been reported.

AIT may develop both in a normal thyroid gland or in a gland with pre-existing abnormalities. Humoral thyroid autoimmunity seems to play little role in the development of thyrotoxicosis in patients without underlying thyroid disorders.

A possible pathogenic hypothesis suggests that thyrotoxicosis is due to excessive thyroid hormone synthesis induced by the iodine load. In those patients with underlying thyroid disorder and residing in a mildly iodine deficient area, the thyroid gland may fail to adapt normally to the excess iodine load during amiodarone therapy, maybe because of the presence of autonomously functioning nodules resulting in inappropriate elevated radiiodine uptake values. That subgroup of AIT patients usually have normal or slightly elevated serum interleukine-6 (IL-6) levels.

The form of AIT with an underlying thyroid disease, normal/elevated radioactive iodine uptake (RAIU) values, normal/slightly elevated serum IL-6 levels, color flow Doppler sonography patterns (patterns I-III) associated with a hypofunctioning gland with hypervascularity and due to excessive thyroid hormone synthesis has been defined as type I AIT.

In patients with apparently normal thyroid glands the pathogenetic mechanism is related to a thyroid-destructive process with swelling of follicular cells, vacuolisation of the cytoplasm and fibrosis at the histopathological examination and associated leakage of preformed hormones from damaged follicles. That form of thyroid dysfunction following amiodarone therapy has been defined as type II AIT.

Type I AIT is more common in iodine-deficient parts of the world like Europe while type II AIT is more frequent in iodine-sufficient area of the world like United States and United Kingdom.

Nevertheless definitions of AIT may not be so absolute and in fact mixed forms often exist, in which different features of type I and type II AIT may be present.

Clinical Manifestations

In patients presenting AIT the classical symptoms of thyrotoxicosis may be absent, due to an-
tiadrenergic action of amiodarone and its impairment of conversion of T4 to T3. Goiter may be present or absent, with or without pain in the cervical region; ophthalmopathy is often absent, unless AIT occurs in a patient with Graves’ disease.

Physicians can suspect an AIT condition by a worsening of the underlying cardiac disorder with tachyarrhythmias or angina during amiodarone treatment.

The occurrence or recurrence of tachycardia or atrial fibrillation in a patient treated with amiodarone should be considered a good reason to investigate thyroid function.

Physicians should make efforts to differentiate between the two types of AIT because those two types of AIT will be treated differently. However, this may prove very difficult in clinical practice because in general laboratory studies of thyroid function do not discriminate type II AIT from type I AIT: serum free T4 levels are elevated, TSH levels are suppressed, and serum T3 levels may be normal or elevated (Table IV).

Serum thyroglobulin (TG) may markedly increase in AIT patients for increased production and for amiodarone-induced follicular damage.

Otherwise, few elements may drive physicians to differential diagnosis between type I and type II type of AIT: antithyroid antibodies are more often positive in type I AIT than in type II; the levels of serum IL-6 has been reported to be normal or only minimally elevated in AIT type II whereas it is reputed to be elevated in the AIT type 2 (an inflammatory process).

Color flow Doppler sonography may help to discriminate type I AIT that is associated with a high thyroidal blood flow, from type II AIT characterized by a destructive thyroiditis with a low internal thyroidal blood flow.

### Treatment

#### Type I AIT

In type I AIT the goal of therapy should be to block further organification of iodine and thus to block the synthesis of thyroid hormones. Since the iodine rich thyroid during amiodarone assumption is more resistant to thionamides, larger than usual daily doses of methimazole (40-60 mg) or propylthiouracil (600-800 mg) are often necessary. Another target of the therapeutic strategy is also to decrease the entrance of iodine into thyroid and deplete intrathyroidal iodine stores. The latter effect can be achieved by potassium perchlorate (1 g daily) that inhibits thyroid iodine uptake.

Simultaneous administration of potassium perchlorate and methimazole is associated with a shorter period of time for the attainment of euthyroidism than in patients responsive to conventional thionamide treatment.

Nevertheless the use of potassium perchlorate is limited by its toxicity particularly agranulocytosis, aplastic anemia and renal side effects. A complete blood count should be done every few weeks in patients receiving thionamide and perchlorate to detect haematological alterations.

#### Type II AIT

In type II AIT thionamide and potassium perchlorate are not considered an appropriate therapy. Because of their membrane-stabilizing, anti-inflammatory effects and inhibition of 5’-deiodinase, steroids are a good and effective therapeutic strategy.

Steroids have been used in type II AIT at different doses (15-80 mg prednisone or 3-6 mg dexamethasone daily) and with different time schedules (7-12 weeks).

For the subgroup of patients with mixed forms of AIT, a combination of methimazole, potassium perchlorate, and steroids is probably the most beneficial therapeutic regimen.

### Table IV. Different features of type I and II amiodarone-induced thyrotoxicosis (AIT).

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying thyroid abnormality</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Excessive hormone synthesis</td>
<td>Destructive thyroiditis</td>
</tr>
<tr>
<td>Thyroidal radioiodine uptake</td>
<td>Normal/raised</td>
<td>Low/absent</td>
</tr>
<tr>
<td>Serum IL-6</td>
<td>Normal/Slightly raised</td>
<td>Profoundly raised</td>
</tr>
<tr>
<td>Thyroid ultrasound</td>
<td>Nodular, hypoechoic, volume</td>
<td>Normal</td>
</tr>
<tr>
<td>Color flow Doppler sonography</td>
<td>High thyroidal blood flow</td>
<td>Low thyroidal blood flow</td>
</tr>
</tbody>
</table>

Thyroidectomy may represent a valid option for AIT patients in which withdrawal of amiodarone is not feasible and in those patients resistant to medical treatment, although the underlying cardiac conditions and the thyrotoxic state may increase the surgical risk or even exclude surgery in some patients.

In patients with a history of AIT in whom amiodarone becomes necessary after it has been discontinued, ablation of the thyroid with radioiodine before resuming amiodarone should be strongly considered.

Plasmapheresis aimed at removing the excess of thyroid hormone from the circulation, has been reported to be efficacious but the effect is often transient and followed by an exacerbation of AIT.

Amiodarone-Induced Hypothyroidism (AIH)

Amiodarone-induced hypothyroidism (AIT) occurs more frequently than AIT in iodine-sufficient areas. In contrast to AIT, AIH is slightly more frequent in females, with a M:F ratio of 1:1.5. AIH patients are older than AIT ones and AIH usually develops earlier than AIT in patients with preexisting thyroid abnormalities.

In the study of Trip et al, female sex or the presence of circulating anti-thyroid peroxidase (TPO) antibodies represented a relative risk of 7.9 and 7.3 respectively for the occurrence of AIH and the combination of female sex and antithyroid antibodies increased the risk to 13.5.

Baseline elevation of TSH before starting amiodarone has also been shown to be a risk factor for the development of AIH, probably reflecting underlying autoimmune thyroid disease.

Furthermore there was no difference in the daily amiodarone dose or its serum concentrations between euthyroid patients and those who developed hypothyroidism.

The most likely pathogenic mechanism is that the thyroid gland of these patients damaged by preexisting Hashimoto’s thyroiditis, is unable to escape from the acute Wolff-Chaikoff effect after an iodine load and to resume normal thyroid hormone synthesis and the inability to escape from the acute Wolff-Chaikoff effect.

In AIH patients without underlying thyroid abnormalities and with negative thyroid autoantibody tests, subtle defects in iodine organification and thyroid hormone synthesis are likely the best explanation for the occurrence of AIH. It has been reported that AIH may spontaneously remit after discontinuation of amiodarone treatment within 2-4 months.

Clinical Manifestations

AIH typically occurs between 6-12 months of treatment with amiodarone and AIH patients frequently have vague symptoms and signs like fatigue, lethargy, cold intolerance, mental sluggishness, and dry skin. Myxedema coma has been reported in a patient taking amiodarone.

In patients already on L-T4 replacement therapy, the dose of L-T4 may need to be increased due to the inhibition of the generation of T3 from T4 induced by amiodarone.

Laboratory tests show decreased serum free T4, increased serum TSH concentrations and increased serum thyroglobulin because of the enhanced thyroid stimulation by TSH.

Serum thyroglobulin is often increased, probably because of the enhanced thyroid stimulation by TSH.

Treatment

If amiodarone can’t be discontinued for underlying cardiac disorder, it can be continued in association with L-T4 replacement which requires once-daily administration. The serum TSH concentration is the most important parameter to monitor therapy and adjusting the dosage of L-T4.

Low-dose L-T4 therapy can be initiated, starting with 25-50 µg/die. Serum TSH levels should be assessed after 4-6 weeks, and the LT4 dose increased slowly until the serum TSH has returned to normal values. The dose of L-T4 needed to normalize serum TSH may be higher in amiodarone-treated patients compared with conventional hypothyroid patients, possibly the result of decreased intrapituitary T3 production due to inhibition of pituitary type II 5'-deiodinase.

If discontinuation of amiodarone is feasible, spontaneous remission of hypothyroidism often
occurs within 2-4 months, particularly in patients without underlying thyroid abnormalities, while this outcome is less likely to occur in patients with Hashimoto’s thyroiditis.

Thyroxine therapy can be administered if the patient is symptomatic but, because hypothyroidism may resolve in patients without underlying thyroid autoimmunity, patients should be re-evaluated after 6-12 months of therapy to determine the continuing need for LT4 therapy.

Amiodarone in Pregnancy

Mild mental retardation and impaired speech and language skills were reported in only a few children exposed to amiodarone in utero. Hence, amiodarone can reasonably be administered to pregnant women if they have life-threatening or refractory arrhythmias that are resistant to other anti-arrhythmics. Serial sonograms should be performed to detect fetal goiter. Iodine-induced goiter, with or without hypothyroidism, can cause severe dyspnoea in newborns.

If a goiter is seen, intra-amniotic LT4 therapy should be considered because it has been shown to be effective.

If a mother decides to breast feed while on amiodarone, serial evaluation of thyroid function tests should be performed in the infant, and appropriate treatment promptly initiated if hypothyroidism develops.

Monitoring Thyroid Function in Patients Taking Amiodarone

Baseline thyroid function testing should be undertaken before starting treatment and should include thyroid ultrasonography, serum TSH and thyroid antibodies. Patients with pre-treatment normal-high levels of serum TSH and/or thyroid antibodies and thyroid ultrasound pattern of Hashimoto’s thyroiditis are at increased risk of developing hypothyroidism and require close follow-up. Those patients with nodular goiter seen at thyroid ultrasound and/or with low TSH concentrations are probably at increased risk of developing type I AIT.

Serum TSH concentrations should be measured every six months during treatment primarily to permit the identification of hypothyroidism (see Figure 1). If equivocal biochemical results are obtained in clinically euthyroid patients, suggestive of subclinical hypothyroidism or thyrotoxicosis, then further testing in six weeks is recommended. The presence of thyroid antibodies in patients with a moderately raised TSH is a strong supportive evidence of hypothyroidism and probably merits treatment with T4 without further delay.

Type II AIT has an explosive onset, and is difficult to predict, while type I AIT can occur months or even years after discontinuation of amiodarone therapy. Some patients with treated type II AIT will eventually become hypothyroid due to extensive damage to thyroid tissue, as will some type I AIT patients treated with radioiodine.

Careful and prolonged monitoring of thyroid function in all patients with history of thyrotoxicosis is therefore mandatory, even after amiodarone is withdrawn.

Patients should be counseled regarding the symptoms of hyperthyroidism and hypothyroidism and, once thyroid dysfunction is detected, the patients should be referred to an endocrinologist for evaluation.
Conclusions

Amiodarone is a very effective antiarrhythmic drug, widely used in clinical practice for tachyarrhythmias. Physician should know that its use is associated with variations in thyroid function tests that don’t reflect true changes in thyroid function. However a group of amiodarone treated patients develop either hypothyroidism or thyrotoxicosis in apparent normal glands or in glands with preexisting abnormalities.

The follow-up and clinical monitoring of thyroid status in patients undergoing chronic treatment with amiodarone is mandatory in order to diagnose as soon as possible a starting amiodarone-induced thyroid dysfunction.

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Amiodarone-induced thyroid dysfunction in clinical practice


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