Amiodarone as a double-edged sword: Anti-arrhythmic agent versus drug-induced thyrotoxicosis

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ABSTRACT
Amiodarone is widely used in the treatment of paroxysmal atrial tachycardia, atrial fibrillation, recurrent severe ventricular arrhythmias and maintenance of sinus rhythm following cardioversion. Amiodarone-induced thyrotoxicosis, types I and II, is a known adverse effect occurring in up to 3% of patients. Treatment depends on sub-type and aetiology, whilst further management of the underlying arrhythmia may be difficult.

Keywords:
amiodarone, thyrotoxicosis, atrial fibrillation, ventricular tachycardias, hypothyroidism

Abbreviations:
AF – atrial fibrillation
AIT – amiodarone induce thyrotoxicosis
ECG - electrocardiogram
TFT – thyroid function test
TSH – thyroid stimulation hormone
1. CASE PRESENTATION

We present two cases of amiodarone-induced thyrotoxicosis occurring in our national hospital within a short time of each other.

Case 1: A 68-year old gentleman, known case of refractory atrial fibrillation (AF) awaiting ablation being treated with amiodarone, atenolol and warfarin, presented with a two week history of constant palpitation associated with exertional dyspnoea and transient chest pain. He was haemodynamically stable though oxygen saturation was 93% on room air. On examination he had mild bibasal crepitations, with clinical examination being otherwise unremarkable. ECG showed AF at 128 beats per minute. He was admitted for DC cardioversion but reverted spontaneously to normal sinus rhythm with prolonged QTc pending the procedure. Amiodarone and atenolol were therefore stopped and diltiazem started. The patient subsequently reverted back to fast AF and was once again switched to amiodarone. Thyroid function tests taken during admission revealed severe hyperthyroidism with a free T4 greater than 77.20 pmol\(^{-1}\) and TSH of 0.036 mIU\(^{-1}\). Amiodarone was therefore stopped and patient referred urgently to an endocrinologist. He was started on both prednisolone 35 mg daily and carbimazole 40 mg daily. These were tailored off over four months. Diltiazem 60 mg eight-hourly was also given as rate-controlling agent. The patient underwent successful AF ablation and has since remained in sinus rhythm.

Case 2: A 36-year old gentleman with a history of right ventricular outflow tract ventricular tachycardias, tachycardia cardiomyopathy with secondary congestive heart failure and CRT-D implantation, bronchial asthma and obstructive sleep apnoea, presented with dyspnoea and worsening lower limb oedema despite increasing doses of diuretic. He was haemodynamically stable and had mild bibasal crepitations and bipedal oedema, with clinical examination being otherwise unremarkable. ECG showed paced beats with frequent ventricular ectopics, at 120 beats per minute. He was unsuccessfully treated for CHF exacerbation with intravenous diuretics. Thyroid function tests taken during admission revealed severe hyperthyroidism with a free T4 greater than 77.20 pmol\(^{-1}\) and TSH of less than 0.004 mIU\(^{-1}\). Ultrasound scan of the thyroid showed a diffusely enlarged thyroid gland with reduced vascularity consistent with type II amiodarone induced thyroiditis. Amiodarone was immediately stopped and the patient referred urgently to an endocrinologist. Treatment with carbimazole and prednisolone was commenced, whilst nebivolol was started as an anti-arrhythmic agent, given the patient’s history of asthma. Long-term management was by VT ablation.

2. DISCUSSION

2.1. Structure and iodine content of Amiodarone

Amiodarone is a benzofuran derivative containing organic iodine in the range of 37.5% by molecular weight, one-tenth of which is converted to free iodine. Normal daily maintenance doses (200–400 mg) generate about 6–12 mg of free iodine per day, resulting in an intake of iodine that is 40 times that suggested by the World Health Organisation. Furthermore, Amiodarone is stored in various organs and has an elimination half-life of about 2–3 months (Keh-Chuan Loh, 2000).

2.2. Pharmacology of Amiodarone

Amiodarone is a Vaughan-Williams class III anti-arrhythmic agent widely used in the treatment of paroxysmal atrial tachycardia, atrial fibrillation, recurrent severe ventricular arrhythmias and maintenance of sinus rhythm following cardioversion (Goldschläger et al. 2000). It acts as a smooth muscle relaxant, causes a mild elevation in cardiac index and reduces afterload by decreasing peripheral vascular resistance (NCBI 2014, www.drugbank.ca 2014). As a Class III agent, its main pharmacological effect on the cardiac action potential is prolongation of phase 3. Amiodarone, however, is unique in that it has also effects that are similar to class Ia (acting on fast sodium channels, with increasing effect at increased heart rates), class II (antisympathetic properties via α- and β-adrenergic receptors), and class IV (via L-type calcium channel blockade) anti-arrhythmic drugs (www.drugbank.ca 2014, Martino E et al. 1984); it acts on the sino-atrial and atrio-ventricular nodes similar to beta and calcium-channel blockers, whilst acting on potassium and sodium channels, increasing cardiac refractory period and delaying intra-cardiac action potential.

2.3. Amiodarone-induced thyrotoxicosis

Type I and II

Amiodarone-induced thyrotoxicosis, is a known adverse effect occurring in up to 3% of patients (Martino et al. 1984). In addition, more than half of patients receiving amiodarone experience some degree of derangement in their thyroid function test, namely mild increase in free serum T4 and reverse T3, marginal elevation of T3 and / or transient changes in thyroid stimulating hormone. Such derangement, however, is usually sub-clinical and hence patients do not manifest any signs or symptoms. Hypothyroidism may also result from the use of amiodarone, with persistent and
gradually increasing thyroid stimulation hormone levels being a warning sign, especially as hypothyroidism usually presents subtly. Thyrotoxicosis, in contrast, develops acutely, with clinical manifestations that may be life threatening. It may not occur at initiation of treatment and may in fact develop even after two to three years (Han et al. 2009). Patients may present with signs of hyperthyroidism such as weight loss, muscle weakness, low grade fever, loose bowels, tremor, mood changes, heat intolerance, goitre and palpitations. As occurred in the first of our cases, the thyrotoxic state itself may paradoxically precipitate cardiac arrhythmias, including atrial fibrillation and ventricular tachycardias. The patient may have been started on amiodarone to correct such abnormal electrophysiology in the first place, and the physician should therefore evaluate the possibility of amiodarone-induced thyrotoxicosis in patients previously stabilised on amiodarone.

Amiodarone-induced thyrotoxicosis is more common in men (ratio 3 : 1). Two sub-types have been described, depending on aetiology. These are referred to as types I and II. Epidemiological data shows that type I predominates in poor areas where patients are more likely to suffer from iodine-deficiency, whilst type II is more common in North America.

Type I occurs in patients with underlying thyroid pathology such as Graves’ disease or autonomous nodular goiter (Tsang et al. 2009). The increased intake of iodine, contained in the drug itself, results in increased thyroid hormone synthesis. This pathophysiology is called the Jod-Basedow phenomenon whereby the iodine overload elicits an autonomous response by the thyroid tissue, caused by excessive and uncontrolled biosynthesis of thyroxine.

Type II thyrotoxicosis occurs in patients with a previously healthy thyroid gland. The direct toxic effect of amiodarone on thyroid follicular cells leads to destructive thyroiditis. Such process is mediated by the release of mitochondrial cytochrome c that results in apoptosis via an iodine-induced mechanism. This in turn results in excessive release of preformed T4 and T3 into the circulation (Cardenas et al. 2003). Such effect is long-lasting, with duration of up to a few months, following which the patient may become hypothyroid. Complete recovery eventually occurs in the vast majority of patients (Tsang et al. 2009).

Distinguishing between the two forms is important as management differs. Careful history and physical examination may indicate or otherwise pre-existing thyroid pathology (Tsang et al. 2009), whilst Colour flow Doppler ultrasonography of the thyroid may further aide characterisation (Loy et al. 2007). Hans et al. (2009) describe response to treatment as a way of distinguishing between the two (see figure 1). A more holistic approach, put forward by Cardenas et al. (2003), suggests “establishing a diagnosis by assigning a relative weight to all available information”. The criteria that may be used to differentiate between the two types of AIT are summarised in Table 1.

2.4. Management
The treatment of Amiodarone-induced thyrotoxicosis (AIT) presents a two-fold challenge, to endocrinologist and cardiologist alike. Firstly, difficulty with distinguishing between types I and II may be reflected in more complex management, whilst both the long half-life and accumulated iodine stores increase the duration of adverse effects and provide resistance to treatment. Secondly, management of the underlying arrhythmia is also challenging, given that such arrhythmia would have usually been well controlled on Amiodarone, sometimes for years.

Hans et al. (2009) suggests three initial management steps: Stopping Amiodarone immediately, starting Carbimazole (40 mg daily) and starting Prednisolone (40 mg daily). T3 levels should then be rechecked at day 14 from commencement of treatment. If this is increased or remains unchanged, then a diagnosis of type I AIT can be made and the patient continued on Carbimazole whilst stopping prednisolone. If T3 levels decrease by at least 50%, on the other hand, the patient is said to suffer from type II AIT and should continue receiving prednisolone but not Carbimazole. In either case treatment may be required long-term, even up to months after stopping amiodarone.

2.5. Alternative Anti-Arrhythmic Drugs
Management of the underlying arrhythmia following amiodarone-induced thyrotoxicosis has received little attention. Amiodarone is almost invariably stopped at diagnosis of such adverse effect. The choice of alternative agent depends on the underlying rhythm. In atrial fibrillation, sole rate control with drugs such as digoxin, beta-blockers or calcium antagonists remains an option. If rhythm control is required, however, sotalol and dronaderone provide good alternatives. Nebivolol was the drug of choice in our second patient in view of his history of asthma.

In patients with ventricular tachycardias, sotalol may also be used. Other drugs to consider include verapamil and flecainide.

Another option is ablation of the thyroid gland using radioiodine. Hermida et al. (2004) concluded that “131I therapy appears to be an effective and safe approach to prevent the recurrence of AIT in a patient requiring the reintroduction of amiodarone for tachyarrrhythmias” (Gilbert, 2000). Such an alternative may be worth considering in patients who were well controlled with amiodarone but not so effectively with other anti-arrhythmic agents. Radiofrequency ablation remains one the best bets in controlling underlying electrical abnormalities without further adverse drug effects.
2.6. Routine monitoring of thyroid function

All patients due to start receiving amiodarone should have their baseline thyroid function assessed prior to starting treatment. If any pre-existing derangement is identified, then amiodarone should either be withheld or given with greater caution and tighter monitoring of thyroid function, due to increased predisposition to hypo- or hyperthyroidism. Thyroid investigations should be repeated after three months, then periodically as deemed necessary. Changes in thyroid stimulation hormone level are usually the sign and should therefore not be overlooked.

SUMMARY

1. Amiodarone is widely used in the treatment of paroxysmal atrial tachycardia, atrial fibrillation, recurrent severe ventricular arrhythmias and maintenance of sinus rhythm following cardioversion.
2. Amiodarone may cause both hypothyroidism and thyrotoxicosis. The latter, occurring in up to 3% of patients, is classified in types I and II, depending on aetiology.
3. Management of amiodarone-induced thyrotoxicosis including stopping the drug as well as prescribing prednisolone and/or carbimazole, depending on the sub-type.
4. Further management of the underlying rhythm is challenging and includes alternative anti-arrhythmic agents, radio-iodine ablation of the thyroid and cardiac radiofrequency ablation.

FUTURE ISSUES

More in-depth analyses of the management of atrial fibrillation and ventricular tachycardias in subjects affected by amiodarone-induced thyrotoxicosis shall aid and provided better guidance to cardiologists and physicians in the management of such patients.

DISCLOSURE STATEMENT

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**Table 1**
Criteria for differentiation between AIT types I and II (Gilbert H. Daniels, 2000, Cardenas et al., 2003)

<table>
<thead>
<tr>
<th></th>
<th>AIT Type I</th>
<th>AIT Type II</th>
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<tbody>
<tr>
<td>Baseline thyroid function tests</td>
<td>Deranged</td>
<td>Normal</td>
</tr>
<tr>
<td>Thyroid autoantibodies</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Goitre</td>
<td>Present</td>
<td>Absent or minimal</td>
</tr>
<tr>
<td>Ultrasound thyroid</td>
<td>Diffuse or nodular goitre</td>
<td>Normal</td>
</tr>
<tr>
<td>Colour flow Doppler</td>
<td>Normal or increased flow</td>
<td>Decreased flow</td>
</tr>
<tr>
<td>Radioactive iodine uptake</td>
<td>Normal or high</td>
<td>(Very) low</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Responds to carbimazole</td>
<td>Responds to steroids</td>
</tr>
</tbody>
</table>

**Figure 1**
Management of AIT: Defining sub-type according to treatment response. From Han T.S., Williams GR, Vanderpump MP 2009, Benzofuran derivatives and the thyroid. Clin Endocrinol (Oxf) 70:2–13.