INVESTIGATION AND MANAGEMENT OF AMIODARONE-ASSOCIATED THYROID DISEASE

BACKGROUND
The recommended daily intake of iodine is approximately 0.2mg/day. A maintenance dose of 200-600mg amiodarone a day will provide 7-21 mg iodide/day. The associated increase in the iodine pool changes thyroid hormone dynamics, although this is not always accompanied by overt thyroid dysfunction.

EFFECTS OF AMIODARONE ON THYROID PHYSIOLOGY
- >50% patients on long-term amiodarone have abnormal TFTs
- Inhibition of type 1 5’-deiodinase enzyme results in decreased peripheral conversion of T4 to T3.
- Entry of T3 and T4 into peripheral tissues is inhibited.
- These effects result in a rise in FT4 and a fall in TT3.
- TSH rises in the first 3 months of amiodarone treatment (due to inhibition of T4→T3 conversion in the pituitary) but TSH often normalises after 3 months.

IODINE AND AUTOREGULATION OF THYROID FUNCTION
- Usually, expansion of the iodine pool causes an autoregulatory decrease in iodine transport and decreased thyroid hormone synthesis to protect against a surge in iodine-driven thyroid hormone synthesis. This protective mechanism is known as the Wolff Chaikoff effect.
- Failure to escape the Wolff Chaikoff effect leads to hypothyroidism.
- If these autoregulatory effects are absent or defective, the thyroid is not buffered from the effects of excessive iodine. Iodine-driven thyrotoxicosis in a previously normal gland is known as the Jod Basedow effect (Jod being the German word for iodine).
- This explains how the same stimulus of an increased iodine load can result in both hypothyroidism and hyperthyroidism

AMIODARONE-ASSOCIATED THYROID DYSFUNCTION
- Approximately 2% patients taking amiodarone develop amiodarone-induced thyrotoxicosis (AIT) (Range 1-23% in different studies).
- Approximately 13% patients taking amiodarone develop amiodarone-induced hypothyroidism (AIH) (Range 1-32% in different studies).
- AIT is more common in areas of low iodine intake.
- AIH is more common in areas of high iodine intake.
AIH

- May be caused by failure to escape the Wolff Chaikoff effect, but gender and thyroid antibodies are also implicated in the pathogenesis of AIH.
- Women with pre-existing thyroid antibodies have a relative risk of developing AIH of 13.5 compared to antibody-negative men.
- AIH may be transient or permanent but it is rare for it to occur after the first 18 months of treatment with amiodarone.
- Permanent AIH after withdrawal of amiodarone is almost always associated with underlying thyroid disease (eg Hashimoto’s).
- Family history of thyroid disease may predispose to development of AIH.
- It has been suggested that baseline TSH is higher in amiodarone-treated patients who develop AIH than in those who remain euthyroid but there is considerable overlap between groups so baseline TSH cannot reliably be used to predict AIH.

Investigation and management

- A raised TSH in the first few months of amiodarone therapy does not necessarily indicated thyroid disease as this can be physiological and self-limiting.
- Treatment of AIH is relatively straightforward and may involve stopping/decreasing amiodarone, administering thyroxine or both.
- The aim of treatment is to keep FT4 at upper end of normal rather than to achieve normal TSH values (much higher thyroxine doses needed for the latter).
- Perchlorate can discharge inorganic iodine and block further entry of iodide into the thyroid gland. Short-term administration of perchlorate rapidly restores thyroid function in small studies of AIH.
AIT

- Unlike AIH, AIT is more common in men (male:female ratio of 3:1).
- AIT may occur one year after drug withdrawal (long drug half-life).
- Classical symptoms may be absent due to amiodarone’s anti-adrenergic effects.
- Raised FT4 alone does not confirm thyrotoxicosis as a slightly raised FT4 and a slightly low TT3 can be physiological.
- In true AIT, the TSH should be suppressed and the TT3 is usually elevated.
- AIT can be divided into types 1 and 2 (table 1). The type affects management.

- There are 3 questions to consider when deciding on management:
  1. **Can amiodarone be stopped?** The following factors are relevant:
     a. $t/2$: Its long half-life (22-55 days) means that discontinuation will not rapidly provide a solution to the AIT.
     b. Indication: e.g. if amiodarone has been given to treat a ventricular arrhythmia it is unlikely that it can be stopped.
     c. Cardioprotection: amiodarone’s anti-adrenergic effects paradoxically confer a degree of protection on the heart by limiting AIT-induced tachycardia
     d. In a retrospective case series (n=28) where those with ventricular arrhythmias continued amiodarone (n=16), there was no difference between the two groups in the dose of carbimazole required, the rate of recovery of TFTs, the development of spontaneous euthyroidism or the subsequent relapse of AIT.
  2. **Is antithyroid Rx needed?** If thyrotoxicosis is mild and amiodarone can be discontinued, it may be worth holding off antithyroid treatment.
  3. **If treatment is needed, which is most appropriate?** (Consider aetiology)
     a. **Type 1 AIT: ATDs** can be used but high doses are required. This decreased efficacy may relate to high intrathyroidal iodine stores. 1g/day potassium perchlorate till the patient is euthyroid (maximum 6/52) can help discharge iodide stores and prevent further uptake of iodide by the thyroid. Side-effects include aplastic anaemia and nephrotic syndrome so FBC and U/E should be monitored. Carbimazole doses often need to start at 40-60mg (or 400-600mg PTU daily).
     b. **Type 2 AIT: Prednisolone** inhibits 5 prime-deiodinase activity and may also have direct effects on the thyroid gland.
     c. I131 not usually useful (high iodide suppresses I131 uptake). However, occasionally in type 1 AIT, iodine uptake is sufficient to allow treatment.
Table 1

<table>
<thead>
<tr>
<th></th>
<th>AIT type I</th>
<th>AIT type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetiology</td>
<td>Iodine toxicity causes excess thyroid hormone synthesis, often in those with underlying autoimmune thyroid disease</td>
<td>Destructive thyroiditis</td>
</tr>
<tr>
<td>Goitre</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Antibodies</td>
<td>May be +ve but not consistently so in all studies (may be more important in those with underlying thyroid disease)</td>
<td>-ve</td>
</tr>
<tr>
<td>I131 uptake</td>
<td>Normal/slightly ↑</td>
<td>Decreased</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>Normal/slightly ↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>IL6</td>
<td>Normal</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Does not occur</td>
<td>Late hypothyroidism is possible</td>
</tr>
<tr>
<td>Doppler</td>
<td>↑/N vascularity</td>
<td>↓ vascularity</td>
</tr>
<tr>
<td>Treat AIT</td>
<td>Potassium perchlorate and ATDs</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Definitive</td>
<td>Thyroidectomy (I131)</td>
<td>Follow up for possible late hypothyroidism. Consider thyroidectomy if prednisolone fails</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALGORITHM FOR INVESTIGATION AND MANAGEMENT OF AIT

1. **Confirm that it is true AIT:**
   a. Are there clinical signs to suggest AIT (though amiodarone may mask ↑HR).
   b. Check TSH and TT3 as raised FT4 alone could be physiological.

2. **Establish aetiology (type 1/type 2/mixed)**
   a. Is there a goitre? Are antibodies positive?
   b. Doppler or uptake scan may help. IL-6 not routinely available and thyroglobulin results are not rapidly available.

3. **Consider whether amiodarone can be stopped in consultation with cardiology**

4. **If antithyroid treatment required, give potassium perchlorate and ATDs for type 1, prednisolone for type 2 and both for mixed forms.**

5. **If medical therapy fails or if amiodarone cannot be discontinued, thyroidectomy may need to be considered** (caution with pre-operative beta blockade due to anti-adrenergic effects of amiodarone).
REFERENCES

