The Journal of Laryngology & Otology (2009), ***123***, *1276–1279*.

doi:10.1017/S0022215108004167

Clinical Record

Surgical management of amiodarone-induced thyrotoxicosis in a patient with Eisenmenger's syndrome: literature review and case report

R Pratap, A Qayyum*, N Ahmad†, P Jani†

Abstract

Objective: We present a patient with a rare combination of amiodarone-induced thyrotoxicosis and Eisenmenger's syndrome.

Method: Case report and review of the world literature regarding the morbidity and mortality of surgical management of amiodarone-induced thyrotoxicosis and the potential hazards of non-cardiac surgery in patients with Eisenmenger's syndrome.

Results: Failure of maximal medical therapy necessitated surgical management to treat amiodarone-induced thyrotoxicosis which, in this particular patient, carried significant risks. Total thyroidectomy was performed leading to rapid resolution of thyrotoxicosis, and the patient made an uncomplicated recovery. We present this case because of its rarity and the potentially hazardous nature of surgical intervention in patients with Eisenmenger's syndrome. The pathogenesis of amiodarone-induced thyrotoxicosis and the differing approaches of medical and surgical management are discussed.

Conclusion: Based on our findings, we propose that surgical management should be considered earlier in the treatment algorithm (or possibly as first-line therapy) for amiodarone-induced thyrotoxicosis.

Key words: Amiodarone; Thyrotoxicosis; Thyroid Surgery; Eisenmenger's Syndrome

Introduction

Amiodarone is a potent antiarrhythmic which has been used in Europe since the 1960s to treat various cardiac arrhythmias, ranging from paroxysmal atrial fibrillation to life-threatening ventricular tachyarrhythmias. Amiodarone use has also been associated with a variety of adverse effects, not least on thyroid function, and can lead to hypothyroidism or thyrotoxicosis in some patients.[1] For patients requiring prolonged therapy, amiodarone-induced thyrotoxicosis is potentially life-threatening in those with significant cardiac comorbidities, and it can pose a challenge to medical management.

In the UK, amiodarone-induced thyrotoxicosis develops in 2 to 3 per cent of patients who have received therapy for an average of 21 months (although there is great variability in treatment duration prior to development of the condition); there is a much higher incidence in iodine-deficient areas.[2] Amiodarone-induced thyrotoxicosis has been subdivided into three entities: type I, type II and a mixed type. Type I amiodarone-induced thyrotoxicosis is due to increased synthesis and secretion of thyroid hormone, in the presence of pre-existing thyroid pathology. Type II amiodarone-induced thyrotoxicosis occurs when a previously normal thyroid gland undergoes changes due to chronic amiodarone therapy, leading to a destructive thyroiditis with subsequent leakage of stored thyroid hormones (but no increase in production). There is no clear consensus on optimal medical management, and total or subtotal thyroidectomy (with its perceived risks) is often reserved as a final option in the treatment algorithm. Of concern is the reported incidence in the world literature of papillary thyroid cancer in patients with type II amiodarone-induced thyrotoxicosis, although whether this is coincidence or association is difficult to ascertain.[3,4]

General anaesthesia for non-cardiac surgery is not undertaken lightly in patients with Eisenmenger's syndrome as there is a significant risk of mortality. It has been suggested that these very patients with congenital cardiac disease, needing prolonged amiodarone therapy, may be at increased risk of developing amiodarone-induced thyrotoxicosis.[5] Furthermore, in view of the increasing use of amiodarone by physicians and the subsequent rise in the incidence of amiodarone-induced thyrotoxicosis, surgeons are likely to encounter this condition more frequently.

Case report

A 39-year-old man with a known history of Eisenmenger's syndrome (i.e. ventral septal defect, atrial septal defect and tricuspid atresia) presented with palpitations, dyspnoea and diarrhoea. He had not required corrective cardiac surgery and had been receiving amiodarone therapy (for 30 months) for paroxysmal atrial fibrillation, in addition to warfarin due to the risk of thromboembolism. There was no other comorbidity and no family history of thyroid or congenital heart disease.

From the Department of Otolaryngology, Norfolk and Norwich University Hospital, the *Department of Otolaryngology, Ipswich Hospital, and the †Department of Otolaryngology, Addenbrooke's Hospital, Cambridge, UK.
Accepted for publication: 11 September 2008. First published online 2 December 2008.

On examination, the patient was anxious, dyspnoeic and peripherally cyanosed, with clubbing (in both hands) in addition to an obvious goitre. Clinical examination revealed severe thyrotoxicosis with a fine tremor and atrial fibrillation (ventricular response 160 beats/minute), but there were no signs of left ventricular failure.

Investigation revealed an erythrocytosis (haemoglobin concentration 20.0 g/dl) and biochemical confirmation of severe thyrotoxicosis (with a free thyroxine (T_4) concentration of greater than 150 pmol/l and a free tri-iodothyronine (T_3) concentration of 39.0 pmol/l). A technetium scan revealed poor thyroid uptake.

Despite withdrawal of amiodarone therapy and treatment with carbimazole (80 mg/day) followed by adjunctive steroids, there was continuing clinical and biochemical thyrotoxicosis, which was cause for increasing concern considering our patient's Eisenmenger's syndrome. Increasing doses of dexamethasone (6 mg/day) and initiation of propylthiouracil (increased to 800 mg/day) led to transient improvement of symptoms but relapse within days. Lithium therapy (a titrated increase to 1.2 g/day) brought no resolution of symptoms, and the patient's free T_4 and free T_3 concentrations reached 150 and 28.2 pmol/l, respectively. After a total of six weeks of attempted medical management, the patient was finally referred for thyroidectomy.

The patient was counselled on the significant risks of the procedure in this particular case, and full multidisciplinary consultation was initiated between the surgeon, endocrinologist, cardiologist and anaesthetists (both in theatre and intensive care), in order to minimise risk to the patient. Potassium percholate, maximal beta-blockade (with propanolol) and heparin infusion therapy was used to optimise the patient's condition prior to surgery, and intensive care was planned post-operatively.

After heavy premedication, an arterial line was inserted to allow rapid monitoring. Using careful titration, sodium thiopentone was used for induction of anaesthesia with paralysis by vecuronium. Intravenous opioid (remifentanil) was used to maintain anaesthesia, with inhalation of enflurane to prevent awareness and crystalloids for fluid replacement.

A total thyroidectomy was performed, with meticulous haemostasis to minimise blood loss and blood sampling to monitor serum free T_4 throughout the procedure. The patient did not suffer any intra- or post-operative complications. Post-operatively, there was rapid resolution of amiodarone-induced thyrotoxicosis, both clinically and biochemically.

Histological examination of the resected thyroid confirmed the presence of changes consistent with amiodarone-induced thyrotoxicosis. There was no evidence of malignancy.

Literature review

A literature review was undertaken to assess the reported morbidity and mortality associated with non-cardiac surgery for Eisenmenger's syndrome and amiodarone-induced thyrotoxicosis. In view of continuing controversies and difficulties in the diagnosis and medical management of our patient's amiodarone-induced thyrotoxicosis, the alternative option of surgery for amiodarone-induced thyrotoxicosis was evaluated.

A Medline literature search was performed of articles from 1975 to the present, using combinations of the following keywords: 'amiodarone', 'thyrotoxicosis', 'surgery and Eisenmenger's syndrome' and 'surgery'. Articles referring to non-cardiac surgery for Eisenmenger's syndrome were then manually selected. Analysis was also performed on selected case series to determine significant morbidity and mortality associated with surgical management of amiodarone-induced thyrotoxicosis.

A number of papers had been published on non-cardiac surgery in both adult and paediatric patients with Eisenmenger's syndrome. We reviewed a total of 19 non-cardiac procedures described in the world literature, involving 16 patients.[5–10] In total, eight patients (undergoing 11 procedures) were children and eight were adults. No patients were older than 40 years, and none had thyroid pathology. A large variety of anaesthetic techniques were employed, ranging from xenon gas to the use of different intravenous agents. A common theme throughout the various studies was careful patient selection, intensive monitoring and maintenance of systemic vascular resistance and blood pressure. Apart from two documented episodes of transient bradycardia,[6,7] general anaesthesia was well tolerated; no intra-operative mortality was recorded. Two patients had post-operative complications related to the surgical procedure (i.e. glossopharyngeal nerve palsy and hoarseness of voice); no complication could be attributed to the general anaesthetic.[7,8] No post-operative deaths were recorded, despite some patients undergoing major procedures.

A number of case series have been published detailing the surgical management of amiodarone-induced thyrotoxicosis. Apart from our own patient, analysis of 110 cases of surgery (total or subtotal thyroidectomy) in patients with amiodarone-induced thyrotoxicosis revealed low levels of significant morbidity (7.2 per cent), with two cases each of post-operative lower respiratory tract infection, cardiac dysrhythmia and symptomatic hypocalcaemia. Two further instances of thromboembolic stroke and sepsis were also recorded.[11,12] Until 2004, there was no recorded mortality due to surgery for amiodarone-induced thyrotoxicosis, and even with the three recorded cases in one series at one surgical unit, the overall reported mortality rate was 2.7 per cent.[11] It must be noted that none of these patients had significant congenital cardiac comorbidity prior to surgery.

The majority of patients treated (56 per cent (55/98)) had failed medical therapy prior to surgery. Interestingly, a significant proportion (48 per cent) had surgical intervention as first-line treatment of amiodarone-induced thyrotoxicosis.[11–21] Of the 49 cases in which classification of amiodarone-induced thyrotoxicosis could be ascertained, 14 (29 per cent) were type I and 35 (71 per cent) type II.[12–16,19,21] All patients were treated definitively, resulting in rapid resolution of amiodarone-induced thyrotoxicosis, and there was no reported recurrence in those recommenced on amiodarone therapy.

Discussion

The pathogenesis of amiodarone-induced thyrotoxicosis is not fully understood. Being a fat-soluble drug that contains iodine and having a molecular structure similar to both T_4 and T_3, amiodarone therapy generates immense expansion of both systemic and thyroidal iodine pools. A typical 200 mg dose of amiodarone will cause the release of 100–200 times the recommended daily intake of iodine.[1] Amiodarone also decreases peripheral deiodination of T_4 to T_3, leading to an increase in serum T_4 and a decrease in T_3; these changes, in addition to the cytotoxic effects of amiodarone on thyroid follicles, have been implicated in the pathogenesis of amiodarone-induced thyroid dysfunction.[1,22] Paradoxically, the reduction of peripheral deiodination may result in worsening rebound thyrotoxicosis when amiodarone is withdrawn, due to an increase in T_3. Amiodarone-induced thyrotoxicosis may also sometimes occur after cessation of therapy, due to the long half-lives

https://doi.org/10.1017/S0022215108004167 Published online by Cambridge University Press

of amiodarone and its metabolite (which can average over three months).[1]

Diagnosis is often delayed due to masking of the clinical features of thyrotoxicosis by the anti-adrenergic effects of amiodarone. However, even when a diagnosis is finally made, treatment is both contentious and challenging. Different authors advocate various medical management regimens, sometimes of dubious efficacy, and there is not even consensus on the importance of determining the type of amiodarone-induced thyrotoxicosis prior to medical therapy.[23–25]

Surgery for amiodarone-induced thyrotoxicosis is usually reserved as a last resort, even though it has been shown to be a rapid, effective and definitive management option, with no risk of recurrence in patients recommencing amiodarone therapy. There are patients who do respond to medical treatment, but in those cases refractory to treatment there is often a delay of weeks or months before surgery is considered.[12,15,21] The potential consequences of delay are brought into sharp perspective by the fact that there is significant cardiovascular morbidity and mortality in those with thyrotoxicosis, particularly in patients with underlying cardiac disease.[26] It is interesting to note that, in the published reports, many patients underwent surgery as first-line treatment of amiodarone-induced thyrotoxicosis; furthermore, in those who did there was no increased morbidity or mortality.[12,17,18] This may be due to there being no pre-operative delay during which cardiac status could worsen.

There is a perception that many patients are simply too 'unfit' for surgery to treat amiodarone-induced thyrotoxicosis, as many have uncontrolled thyrotoxicosis and cardiac failure. Our experience is in agreement with that of the published literature, that is, even in high risk cases (such as our patient with Eisenmenger's syndrome), surgery appears to be a relatively safe option when compared with no treatment or continuation of failing medical therapy.[12,21,27] Based on these findings, we would urge that surgery be considered much earlier in the treatment algorithm; furthermore, we believe a debate needs to be undertaken on whether it should be first-line therapy. We would propose that surgery appears to be a safe, rapidly effective and definitive treatment option that should be used in the first instance, especially in patients who need continuing amiodarone therapy or those in whom prolonged thyrotoxicosis is particularly hazardous.

- **The mechanism of amiodarone-induced thyrotoxicosis is not well understood**
- **Surgical treatment of this condition is often reserved as a last resort**
- **This report discusses the peri-operative management of a patient with coexisting Eisenmenger's syndrome**

Despite the fact that the presence of Eisenmenger's syndrome is often considered sufficient grounds to declare a patient 'unfit for anaesthesia', the literature would indicate otherwise for non-cardiac surgery. As in the case of our patient, with substantial premedication, insertion of an arterial line for rapid blood pressure monitoring and subsequent reduced use of hypotensive anaesthetic agents, it is possible to maintain systemic vascular resistance and to reduce arterial hypoxaemia due to right to left shunting. Prophylactic measures must be (and in our patient's case were) taken against thromboembolism (patients are frequently polycythaemic), both peri-operatively (due to arterial puncture) and post-operatively (due to patients' increased risk).[28]

As long as the principles of adequate pre-operative multidisciplinary consultation are implemented, it is possible to minimise the risk of morbidity and mortality for surgical patients, whether they have amiodarone-induced thyrotoxicosis, Eisenmenger's syndrome or both.

Conclusion

Surgery should be considered the treatment of choice in patients with amiodarone-induced thyrotoxicosis, before full failure of medical therapy occurs, in order to avoid intra-operative anaesthetic complications associated with the cardiovascular complications of the advanced condition.

References

1 Martino E, Bartalena L, Bogazzi F, Braverman L. The effects of amiodarone on the thyroid. *Endocr Rev* 2001; **22**:240–54
2 Figge HL, Figge J. The effects of amiodarone on thyroid hormone function: a review of the physiology and clinical manifestations. *J Clin Pharmacol* 1990;**30**:588–95
3 Cattaneo F. Type II amiodarone-induced thyrotoxicosis and concomitant papillary cancer of the thyroid. *Eur J Endocrinol* 2000;**143**:823–4
4 Saad A, Falciglia M, Steward DL, Nikiforov YE. Amiodarone-induced thyrotoxicosis and thyroid cancer: clinical, immunohistochemical, and molecular genetic studies of a case and review of the literature. *Arch Pathol Lab Med* 2004;**128**:807–10
5 Thorne SA, Barnes I, Cullinan P, Somerville J. Amiodarone-associated thyroid dysfunction: risk factors in adults with congenital heart disease. *Circulation* 1999; **100**:149–54
6 Lyons B, Motherway C, Casey W, Doherty P. The anaesthetic management of the child with Eisenmenger's syndrome. *Can J Anaesth* 1995;**42**:904–9
7 Kraayenbrink MA, Steven CM. Anaesthesia for carotid body tumour resection in a patient with the Eisenmenger syndrome. A case report. *Anaesthesia* 1985;**40**:1194–7
8 Kopka A, McMenemin IM, Serpell MG, Quasim I. Anaesthesia for cholecystectomy in two non-parturients with Eisenmenger's syndrome. *Acta Anaesthesiol Scand* 2004; **48**:782–6
9 Hofland J, Gultuna I, Tenbrinck R. Xenon anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome. *Br J Anaesth* 2001;**86**:882–6
10 Temelcos C, Kuhn R, Stribley C. Sterilization of women with Eisenmenger syndrome: report of 4 cases. *Aust N Z J Obstet Gynaecol* 1997;**37**:121–3
11 Houghton SG, Farley DR, Brennan MD, van Heerden JA, Thompson GB, Grant CS. Surgical management of amiodarone-associated thyrotoxicosis: Mayo Clinic experience. *World J Surg* 2004;**28**:1083–7
12 Hamoir E, Meurisse M, Defechereux T, Joris J, Vivario J, Hennen G. Surgical management of amiodarone-associated thyrotoxicosis: too risky or too effective? *World J Surg* 1998;**22**:537–42, 542–3
13 Mulligan DC, McHenry CR, Kinney W, Esselstyn CB. Amiodarone-induced thyrotoxicosis: clinical presentation and expanded indications for thyroidectomy. *Surgery* 1993;**114**:1114–19
14 Claxton S, Sinha SN, Donovan S, Greenway TM, Hoffman L, Loughead M *et al*. Refractory amiodarone-associated thyrotoxicosis: an indication for thyroidectomy. *Aust N Z J Surg* 2000;**70**:174–8
15 Brennan MD, van Heerden JA, Carney JA. Amiodarone-associated thyrotoxicosis (AAT): experience with surgical management. *Surgery* 1987;**102**:1062–7
16 Bogazzi F, Miccoli P, Berti P, Cosci P, Brogioni S, Aghini-Lombardi F *et al*. Preparation with iopanoic acid rapidly controls thyrotoxicosis in patients with amiodarone-induced thyrotoxicosis before thyroidectomy. *Surgery* 2002;**132**: 1114–17

https://doi.org/10.1017/S0022215108004167 Published online by Cambridge University Press

17 Meurisse M, Detroz B, Messens D, D'Silva M, Zakaria Z, Joris J *et al*. The treatment of amiodarone-induced hyperthyroidism. Is there a place for surgery? *Acta Chir Belg* 1994;**94**:36–41
18 Meurisse M, Hamoir E, D'Silva M, Joris J, Hennen G. Amiodarone-induced thyrotoxicosis: is there a place for surgery? *World J Surg* 1993;**17**:622–6
19 Painvin I, Dupuis JM, Victor J, Rohmer V, Ronceray J, Tadei A. Value of thyroidectomy in amiodarone-induced hyperthyroidism. *Arch Mal Coeur Vaiss* 1996;**89**:445–9
20 Gough IR, Gough J. Surgical management of amiodarone-associated thyrotoxicosis. *Med J Aust* 2002;**176**:128–9
21 Franzese CB, Fan CY, Stack BC. Surgical management of amiodarone-induced thyrotoxicosis. *Otolaryngol Head Neck Surg* 2003;**129**:565–70
22 Chiovato L, Martino E, Tonacchera M, Santini F, Lapi P, Mammoli C *et al*. Studies on the in vitro cytotoxic effect of amiodarone. *Endocrinology* 1994;**134**:2277–82
23 Newman CM, Price A, Davies DW, Gray TA, Weetman AP. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998;**79**:121–7
24 Osman F, Franklyn JA, Sheppard MC, Gammage MD. Successful treatment of amiodarone-induced thyrotoxicosis. *Circulation* 2002;**105**(11):1275–7
25 Loh KC. Amiodarone-induced thyroid disorders: a clinical review. *Postgrad Med J* 2000;**76**:133–40
26 Roffi M, Cattaneo F, Brandle M. Thyrotoxicosis and the cardiovascular system. *Minerva Endocrinol* 2005;**30**:47–58
27 Sutherland J, Robinson B, Delbridge L. Anaesthesia for amiodarone-induced thyrotoxicosis: a case review. *Anaesth Intensive Care* 2001;**29**:24–9
28 Foster JM, Jones RM. The anaesthetic management of the Eisenmenger syndrome. *Ann R Coll Surg Engl* 1984;**66**: 353–5

Address for correspondence:
Mr Asad Qayyum,
16 Lavendon House,
8 Paveley Street,
London NW8 8TJ, UK.

E-mail: asadqayyum@doctors.net.uk

Mr A Qayyum takes responsibility for the integrity of the content of the paper.
Competing interests: None declared