

## CASE REPORT

# Amiodarone-induced Hypothyroidism with EPO-resistant Anemia in a Patient with Chronic Renal Failure

Peter M.S. Chang, Yee-Yung Ng\*

*Department of Medicine, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.*

The overall incidence of amiodarone-induced thyroid dysfunction ranges from 2% to 24%. One third to half of patients with hypothyroidism have anemia due to some decrease in normal red blood cell mass and erythropoietin (EPO) resistance. Therefore, for patients with chronic renal disease under medication with amiodarone, early regular thyroid function test should be checked in order to avoid amiodarone-induced hypothyroidism and EPO-resistant anemia. If amiodarone-induced hypothyroidism and EPO-resistant anemia occur in patients with chronic renal failure, early thyroxine should be given instead of waiting for spontaneous recovery by amiodarone discontinuation only. Here, we report a patient with chronic renal failure who developed EPO-resistant anemia after amiodarone treatment for arrhythmia. The hemoglobin level responded to EPO therapy rapidly after thyroxine administration and amiodarone discontinuation. [*J Chin Med Assoc* 2008;71(11):576–578]

**Key Words:** amiodarone, anemia, erythropoietin, hypothyroidism

## Introduction

Arrhythmia is one of the major causes of morbidity and mortality in patients with chronic renal disease. Therefore, amiodarone, an effective class III antiarrhythmic agent, is often administered to chronic renal failure (CRF) patients with atrial and/or ventricular arrhythmias. Although amiodarone has definite advantage over many other antiarrhythmic agents such as digoxin, disopyramide and procainamide because of no need to adjust dosage in renal failure patients,<sup>1</sup> its common side effect is thyrotoxicosis or hypothyroidism. The overall incidence of amiodarone-induced thyroid dysfunction ranges from 2% to 24%, with most in the range of 14–18%.<sup>2</sup>

On the other hand, recombinant human erythropoietin (rHuEPO) is often used to correct anemia in CRF patients because of the diminished biosynthesis of EPO by the diseased kidney. Does amiodarone-induced hypothyroidism cause EPO resistance in CRF patients who are given rHuEPO? Here, we report a patient with CRF who developed EPO-resistant anemia after

amiodarone treatment for arrhythmia. As far as we know, this is the first case of amiodarone-induced hypothyroidism with EPO-resistant anemia reported.

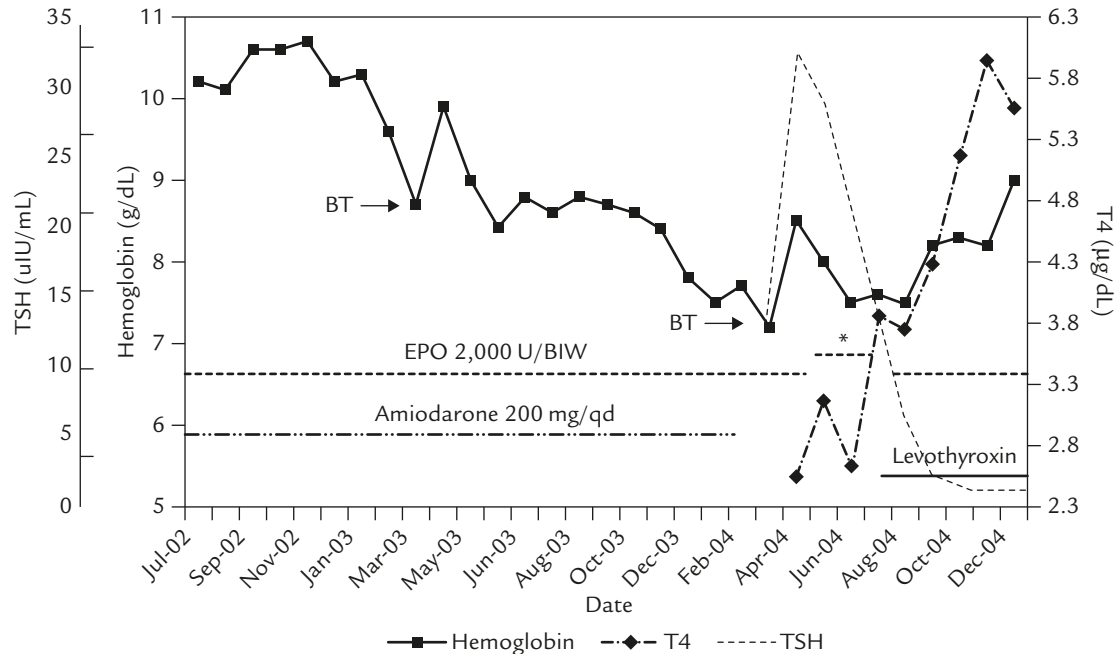
## Case Report

An 83-year-old male had been on oral prednisolone, diuretic, angiotensin-converting enzyme inhibitor (ACEI) and cyclosporin for membranous glomerulonephritis since 1993. Renal function with slowly progressive change was noted during follow-up at the outpatient clinic. He began to be injected with rHuEPO 2,000 U subcutaneously twice a week to improve renal anemia and keep serum hemoglobin level > 10 g/dL in 2000.

After an episode of atrial fibrillation with rapid ventricular response that was corrected by cardioversion in June 2002, oral amiodarone 200 mg daily was given to maintain normal sinus rhythm starting in July 2002. Unfortunately, serum hemoglobin level progressively dropped from above 10 g/dL to 8.5 g/dL without any



\*Correspondence to: Dr Yee-Yung Ng, Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.  
E-mail: [yyng@vghtpe.gov.tw](mailto:yyng@vghtpe.gov.tw) • Received: September 6, 2007 • Accepted: October 21, 2008



**Figure 1.** Clinical course and treatment of amiodarone-induced hypothyroidism with erythropoietin-resistant anemia. Thyroid-stimulating hormone (TSH) level before and after levothyroxin supplement. EPO = erythropoietin; BT = blood transfusion with 2 units of packed red blood cells; T4 = thyroxine. \*Duration of EPO 2,000 U/TIW.

active bleeding source, functional iron deficiency, inflammation or hemolysis in March 2003.

In March 2004, hemoglobin level dropped further to 7.2 g/dL, and the patient received blood transfusion (Figure 1). Laboratory examinations for serum iron, vitamin B12, folic acid, C-reactive protein and hepatoglobulin level were all within normal ranges, except for low serum triiodothyronine level of 45.59 ng/dL (reference range, 60–181 ng/dL), low free thyroxine level of 2.55 ng/dL (reference range, 4.5–12.5 ng/dL), and high thyroid-stimulating hormone (TSH) level of 13.441 uIU/mL (reference range, 0.4–4.0 uIU/mL). Serum intact parathyroid hormone level was 158 pg/mL. Serum calcium and phosphate levels were 7.5 mg/dL and 3.3 mg/dL, respectively. The patient was not on any medication containing aluminum. Therefore, hypothyroidism due to amiodarone was impressed. As hemoglobin level did not increase even after amiodarone was discontinued, rHuEPO was increased to 2,000 U thrice weekly in June 2004.

However, due to the economic burden of rHuEPO 2,000 U 3 times a week and persisting hypothyroidism with no improvement in hemoglobin (thyroxine 3.74 ng/dL and TSH 6.76 ng/dL in August 2004), the dosage of rHuEPO was decreased to 2,000 U twice a week and oral thyroxine was given in September 2004. After the supplement of thyroxine, thyroid function became normal within 3 months (Figure 1). Thyroxine and TSH levels were, respectively, 5.56 ng/dL

and 0.26 ng/dL in December 2004. Hemoglobin level increased rapidly from around 7.5 g/dL to 9.5 g/dL after thyroxine administration (Figure 1).

In August 2002, serum creatinine (Cr) level and creatinine clearance (Ccr) were 4.0 mg/dL and 19 mL/min, respectively. Serum Cr level and Ccr were 5.1 mg/dL and 8.5 mL/min, respectively, in January 2005.

In the following 30 months, ACEI was continuously prescribed, and thyroid function was normal under maintenance thyroxine therapy. Hematocrit was >30% under a dose of rHuEPO 2,000 U twice a week.

## Discussion

Chronic renal disease is often accompanied by normocytic anemia and cardiovascular disease, especially in elderly patients,<sup>3</sup> and EPO therapy has proven to be very effective in the treatment of anemia in patients with CRF. In our patient, rHuEPO 2,000 U subcutaneous injection 2 times a week was initially administrated for renal disease-related anemia, and it could maintain serum hemoglobin level above 10 g/dL. However, hemoglobin level progressively dropped to 7 g/dL from >10 g/dL during amiodarone treatment for atrial fibrillation with rapid ventricular response rate. Evidence that the drop in hemoglobin level was amiodarone-related included: (1) there was no episode of iron deficiency, folate deficiency, vitamin deficiency,

blood loss, inflammation, hypersplenism, hemolysis, severe hyperparathyroidism, aluminum toxicity and hemoglobinopathy;<sup>4</sup> (2) amiodarone-induced hypothyroidism occurs more frequently than amiodarone-induced thyrotoxicosis in iodine-sufficient areas<sup>3</sup> (incidence of amiodarone-induced hypothyroidism is 5–7% and 13–22% in regions with low and high dietary iodine intake, respectively);<sup>5,6</sup> (3) it has been estimated that a third to half of patients with hypothyroidism have some decrease in the normal red blood cell mass;<sup>7</sup> (4) hypothyroidism could also induce EPO resistance;<sup>8</sup> (5) if the severity of anemia is roughly proportional to the degree of azotemia, the hemoglobin level should not increase rapidly after thyroxine supplement; and (6) the dosage of rHuEPO did not increase during medication with thyroxine.

The mechanism of amiodarone-induced hypothyroidism in susceptible patients is thought to result from abnormal response of the thyroid to a chronic high iodine load and then inability to resume normal thyroid function from the inhibitory effect (Wolff-Chaikoff effect) of iodine uptake and hormone synthesis.<sup>9</sup> Because iodine is cleared mainly by the kidneys, patients with CRF may develop thyroid dysfunction when exposed to large doses of iodine.<sup>10</sup> Though the clearance of amiodarone seems not to be influenced in renal failure patients,<sup>1</sup> there were no available data to show the frequency or severity of hypothyroidism if the patient has chronic renal disease and is using amiodarone concomitantly. In this case, diagnosis of amiodarone-induced EPO resistance due to hypothyroidism, the major side effect of amiodarone, was delayed by lack of early regular detection of thyroid function. Thyroxine was also given late due to the wait for the recovery of thyroid function after amiodarone was discontinued.

Therefore, we suggest early regular detection of thyroid function in patients on amiodarone, especially in patients with CRF. Early administration of thyroxine is better than waiting for the spontaneous recovery of thyroid function.

In conclusion, amiodarone-induced hypothyroidism should be put in the differential diagnosis of unexplained progressive EPO-resistant anemia in patients with chronic renal disease. Early thyroxine administration is better than waiting for the spontaneous recovery of thyroid function for hemoglobin improvement in CRF patients with amiodarone-induced hypothyroidism.

## References

1. Bonati M, Galletti F, Volpi A, Cumetti C. Amiodarone in patients on long-term dialysis. *N Engl J Med* 1983;308:906.
2. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. *Endocr Rev* 2001;22:240–54.
3. Parmar MS. Chronic renal disease. *BMJ* 2002;325:85–90.
4. Ng YY, Chow MP, Lyou JY, Hu HY. Resistance to erythropoietin: immunohemolytic anemia induced by residual formaldehyde in dialyzers. *Am J Kidney Disease* 1993;21:213–6.
5. Martino E, Safran M, Lombardi A. Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. *Ann Intern Med* 1984;101:28–34.
6. Newman CM, Price A, Davies DW. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998;79:121–7.
7. Fein HG, Rivlin RS. Anemia in thyroid disease. *Med Clin North Am* 1975;59:1133–45.
8. Dilek M, Akpolat T, Cengiz K. Hypothyroidism as a cause of resistance to erythropoietin. *Nephron* 2002;92:248.
9. Kurnik D, Loebstein R, Farfel Z, Ezra D, Halkin H, Olchovsky D. Complex drug-drug-disease interactions between amiodarone, warfarin, and the thyroid gland. *Medicine* 2004;83:107–13.
10. Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-induced hypothyroidism. *Thyroid* 2001;11:501–10.