



## CASE REPORT

### Change from propylthiouracil to carbimazole proves fatal

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Recent changes in New Zealand have altered the availability of propylthiouracil. It is no longer a 'funded' medication but is only available via an 'Exceptional Circumstances' application to the Pharmaceutical Management Agency (PHARMAC). Because of this a number of patients in our practice were changed from propylthiouracil to carbimazole. We report a patient who developed agranulocytosis following this change in medication which led to her death from *Aspergillus pneumonia*.

#### Case Report

A 77 year old woman was referred to the Waikato Endocrine Unit in November 1999. In 1986 she had a right partial thyroidectomy for a multinodular goitre having previously undergone thyroid surgery 40 years earlier. In 1997 she was admitted with pneumonia complicated by recurrent ventricular tachycardia requiring treatment with amiodarone. An echocardiogram revealed severe left ventricular dysfunction (ejection fraction = 23%). In November 1999 she became thyrotoxic with a free thyroxine (fT4) of 35  $\mu\text{mol/L}$  (normal 10-20  $\mu\text{mol/L}$ ), free triiodothyronine (fT3) of 3.1  $\mu\text{mol/L}$  (3.0-6.0  $\mu\text{mol/L}$ ), and a thyroid stimulatory hormone (TSH) of <0.01 mU/L (0.3-4.0 mU/L). A nodular goitre was palpable. She was started on propylthiouracil 150 mg twice daily and her TSH returned to the normal range. In July, 2000 following changes to the availability of propylthiouracil, she was converted to carbimazole 15 mg daily.

In September 2000 the patient developed a temperature of 39.3°C without a clinical focus of infection, and became unresponsive. She then had a cardiac arrest secondary to ventricular tachycardia requiring cardioversion. The white blood count (WBC) was  $0.5 \times 10^9/\text{L}$  (4.0-11.0  $\times 10^9/\text{L}$ ) with no neutrophils. She was treated with intravenous antibiotics and granulocyte-colony stimulating factor. Blood cultures grew *Streptococcus pneumoniae*. The patient's clinical condition improved and the WBC increased to  $0.8 \times 10^9/\text{L}$  with neutrophils  $0.1 \times 10^9/\text{L}$  at ten days.

At eleven days she again became unresponsive. She was afebrile with no apparent site of infection. CT brain scan revealed a right external capsule infarct. Repeat blood cultures were negative and a chest x-ray was normal. A catheter urine specimen grew heavy *Candida tropicalis*. Intravenous amphotericin was started. Her condition continued to deteriorate and after discussion with the family, treatment was withdrawn. She died seventeen days after admission.

This case was referred to the coroner and a post mortem examination was performed which revealed marked congestion of the lungs with colonizing *Aspergillus*. Examination of the bone marrow revealed a hypocellular marrow with myeloid suppression. The cause of death was attributed to *Aspergillus pneumonia* on a background of myeloid suppression.

#### Discussion

Thyrotoxicosis is a recognized complication of chronic amiodarone therapy with a reported incidence between 2-

12%.<sup>1</sup> Approximately 37% of amiodarone is organic iodide with 10% of this being deiodinated to free iodine. Long term amiodarone use results in high levels of intrathyroidal iodide.<sup>2</sup> Hence high doses of antithyroid medications are needed to treat amiodarone-induced thyrotoxicosis (AIT). While there are no direct comparisons, propylthiouracil has the theoretical advantage over carbimazole and methimazole in that it also prevents the peripheral deiodination of fT4 to fT3 by inhibition of 5' monodeiodinase, and is the 'drug of choice' for AIT.<sup>3</sup> Radioactive iodine is ineffective for AIT. Surgery is the only permanent solution in patients remaining on amiodarone but may be contraindicated if cardiac function is severely compromised.

Agranulocytosis is a life-threatening side effect of both propylthiouracil and carbimazole with a reported incidence of 0.1-0.5%.<sup>4</sup> In a case-cohort study these medications accounted for 23% of cases of drug-induced agranulocytosis (adjusted relative risk, 114.8).<sup>5</sup> Agranulocytosis occurs most commonly in the first three months of treatment but can occur after prolonged treatment. Older age is a risk factor for the development of agranulocytosis and some studies report an increased risk with higher thionamide doses.<sup>4</sup> Low doses of methimazole have a lower incidence of agranulocytosis than propylthiouracil.<sup>6</sup>

The above patient was changed from propylthiouracil to carbimazole, not for medical reasons, but because of difficulties with supply of propylthiouracil in New Zealand. Abbott Laboratories, the supplier of propylthiouracil, became unable to source the product from the manufacturer. A different propylthiouracil product is available from an alternative supplier (Health Support Ltd) but only under section 29 because this product is not registered in New Zealand and therefore cannot be funded. The development of agranulocytosis following this change of medication proved fatal in our patient who had previously been stable on propylthiouracil. PHARMAC have stated they will approve propylthiouracil via an 'Exceptional Circumstances' application if a patient is 'unable to tolerate carbimazole'. Applications are approved, but require significant work from busy staff, and processing of applications can lead to delays in receiving treatment. New Zealand needs an alternative to carbimazole that is readily available. Propylthiouracil is a necessary drug for the management of thyrotoxicosis, as a first line agent in AIT, and as an alternative to carbimazole in other thyrotoxic conditions.

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1. Loh K. Amiodarone-induced thyroid disorders: a clinical review. *Postgrad Med J* 2000; 76: 133-40.
2. Rao RH, McCready VR, Spathis GS. Iodine kinetic studies during amiodarone treatment. *J Clin Endocrinol Metab* 1986; 62: 563-8.
3. Newman CM, Price A, Davies DW et al. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998; 79: 121-7.
4. Bartalena L, Bogazzi F, Martino E. Adverse effects of thyroid hormone preparations and antithyroid drugs. *Drug Safety* 1996; 15: 53-63.
5. Van der Klauw MM, Goudsmit R, Halie MR et al. A population-based case-cohort study of drug-associated agranulocytosis. *Arch Intern Med* 1999; 159: 369-74.
6. Cooper I. Antithyroid drugs. *N Engl J Med* 1984; 311: 1353-62.

