# EXCESSIVE BLOOD LOSS DURING OPERATION IN THE PATIENT TREATED WITH PROPYLTHIOURACIL

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ABSTRACT

A case of bleeding during operation due to propylthiouracil-induced thrombocytopenia is reported.

A 55 year old male who had been treated with propylthiouracil for two months before operation underwent otherwise uneventful cervical laminectomy. Perioperatively he was transfused seven units of whole blood, two units of packed red cells, six units of platelets and two units of fresh frozen plasma for the estimated blood loss of 5500 ml. The patient underwent thyroidectomy without incident 45 days after withdrawal from propylthiouracil. The value of the preoperative coagulation studies of the patient treated with propylthiouracil is discussed.

KEY WORDS: COMPLICATIONS, bleeding, thrombocytopenia, propylthiouracil; BLOOD, thrombocytopenia.

## INTRODUCTION

PROPYLTHIOURACIL THERAPY for thyrotoxicosis has been a well established therapeutic modality for many years. Since Craddack et al reported a case of severe bleeding diathesis caused by propylthiouracil treatment in 1951,[1] similar cases have been reported in medical literature. In 1972, Gotta and his associates reported a case of propylthiouracil-induced bleeding during operation.[2] Their patient developed profuse bleeding during a thyroidectomy. However the patient received no blood transfusions perioperatively. To our knowledge bleeding during operation caused by propylthiouracil therapy which has necessitated perioperative transfusion has not been reported in the literature.

## REPORT OF A CASE

Two months before the present admission a 55 year old male was admitted to the neurosurgical service of St. Louis University Hospital with a six month history of pain in the back of the neck, which occasionally radiated to the right shoulder. A myelogram showed a right extradural defect at C4-5 and C5-6 and he was scheduled for a posterior cervical laminectomy. At that time he was noted to have atrial fibrillation and an enlarged thyroid.

Hyperthyroidism was confirmed by thyroid function studies which showed tri-iodothyronine resin uptake ($T_3U$) of 50.1 per cent (normal 25–35 per cent), total thyroxine by RIA ($T_4$) > 20.0 mcg/dl (normal 4.5–12.5 mcg/dl) thyroid-stimulating hormone (TSH) > 10.0 μU/ml (normal 0–10 μU/ml). The proposed cervical laminectomy was cancelled at that time. He was treated for hyperthyroidism with propylthiouracil 150 mg q.i.d.; propranolol 40 mg q.i.d.; and for atrial fibrillation with digoxin 0.25 mg qd for two months before operation.

The patient was not exposed to any other drugs or to an environmental toxin. On admission, the physical examination revealed a pulse rate of 80/min, a blood pressure of 140/72 mmHg and a normal temperature. No purpuric areas were noted and the remainder of the physical examination was normal.

The preoperative thyroid function tests done the day before operation were within our normal ranges and were as follows: $T_3U$ 36.3 per cent, $T_4$ 11.2 mcg/dl, TSH 1.5 μU/ml. Other laboratory reports, including CBC, urinalysis and liver function tests were within normal limits. A preoperative EKG revealed a persistant atrial fibrillation with a heart rate of 80. Preoperative coagulation studies were not ordered.

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TABLE I

COAGULATION STUDY

| | Day of Operation | 1st Postop Day | | | 2nd Postop Day | |
|---|---|---|---|---|---|---|
| Time | 1900 | 0500 | 1100 | 1447 | 0400 | 1700 |
| Platelet ($\times 1{,}000/mm^3$) | 102 | 90 | 104 | | | 291 |
| PTT (sec) | 32.4 | 30.8 | 30.7 | 28.3 | 29.8 | |
| PT PTA (sec) | 16.1 | 17.1 | 16.3 | 16.2 | 16.2 | |
| CONT (sec) | 14.8 | 14.8 | 15.2 | 13.7 | 15.0 | |
| PAT (%) | 89 | 69 | 84 | 66 | 87 | |

On the second hospital day, the patient was premedicated with an intramuscular injection of morphine sulphate 10 mg, hydroxyzine hydrochloride 50 mg, and glycopyrrolate 0.3 mg. Anaesthesia was induced with thiopentone 250 mg. After the trachea had been intubated, the patient was placed in the prone position with appropriate support. Anaesthesia was maintained with four litres of nitrous oxide and two litres of oxygen supplemented with droperidol and fentanyl. Neuromuscular relaxation was provided by incremental doses of pancuronium. Respiration was controlled mechanically. Excessive bleeding and difficulty in securing a haemostasis were present from the beginning of the operation. The cervical laminectomy was completed in three hours and five minutes. Seven units of whole blood, two units of fresh frozen plasma, six units of platelets, and 2100 ml of 5% dextrose in lactated Ringer's solution were infused. The blood pressure was well maintained between 100 and 120 mmHg systolic and 70 to 80 mmHg diastolic throughout the operation except for one fifteen minute period of hypotension (80/60 mmHg). No bleeding from or haematoma formation at the operative site was observed in the postoperative period. The estimated blood loss was 5500 ml.

He was then transferred to the recovery room where he was transfused with two additional units of packed cells. Seven hours postoperatively in the ICU, the platelet count was $102{,}000/mm^3$, activated partial thromboplastin time (APTT) was 32.4 sec (normal 20.0–36.0 sec), and prothrombin time (PT) was 16.1 sec, 89 per cent of control (normal 70 per cent). (Table I)

On the morning of the first postoperative day, the platelet count was $90{,}000/mm^3$, APTT 30.8 sec, and PT 17.3 sec (69 per cent of the control). Six hours later the coagulation studies were repeated. The platelet count was $104{,}000/mm^3$ with a normal PT and APTT. Propylthiouracil was discontinued on the morning of the second postoperative day on the recommendation of an endocrinology consultant. Ten hours later the platelet count was $291{,}000/mm^3$. (Table I)

Forty-five days after the cervical laminectomy he underwent an uneventful subtotal thyroidectomy under general anaesthesia. Excessive bleeding was not encountered, nor was he transfused. Thee stimated blood loss was 225 ml. Preoperatively the platelet count was $230{,}000/mm^3$. The PT, APTT, fibrinogen, factor VIII, factor VIII antigen, and Von Willebrand factor were measured and found to be within normal limits. At that time he was being given propranolol, digoxin and sodium iodide. Propylthiouracil was not given after the cervical laminectomy.

## DISCUSSION

In our patient, a preoperative platelet count, PT and APTT unfortunately were not obtained and were not measured until seven hours after the operation. By that time the patient had received seven units of whole blood, two units of packed red blood cells, six units of platelets and two units of fresh frozen plasma. After this therapy it is difficult to identify the aetiology of the bleeding during operation. The past medical history, and family history were negative for a congenital bleeding disorder. He had not been on any other medications which might have induced a bleeding tendency.[3]

Our patient had a low platelet count and a borderline PT until the second postoperative day. Despite the bleeding during operation the patient received propylthiouracil 50 mg q.i.d. until the morning of the second postoperative day. At that time it was discontinued. The low

platelet count and slightly prolonged PT were probably due either to propylthiouracil or the blood given perioperatively.

Naeye and Terrien[4] classified haemorrhagic states following propylthiouracil administration into two categories based on the previously reported cases: (1) those that were associated with depression of bone marrow and thrombocytopenia, and (2) those related to hypoprothrombinaemia.

A large number of cases of propylthiouracil-induced hypoprothrombinaemia have been reported in the medical literature. Propylthiouracil-induced hypoprothrombinaemia was the cause of the bleeding reported by Gotta *et al.*[2]

Thrombocytopenia associated with the administration of propylthiouracil is apparently a rare complication.[5–7]

Fewell et al. reported an acute platelet depression during the administration of propylthiouracil.[5] Their patient, a 50 year old male, was given 400 mg of propylthiouracil daily for ten days followed by 300 mg daily for eight days, then maintained on 50 mg of propylthiouracil three times a week. No platelets were seen in the peripheral blood smear following 60 days of treatment. In another case report,[6] platelet depression to 32,000/mm$^3$ occurred after 12 days of therapy with propylthiouracil. His bleeding time was normal, the clotting time was increased. Within forty-eight hours of withdrawal of the drug the platelet count rose to normal levels.

Dilutional thrombocytopenia is another possible cause of the bleeding during operation. Two reasons suggest that this was not the case in our patient. The first reason was that excessive bleeding began immediately following the surgical incision. Secondly, Miller[8] has reported the platelet count to be about 65 per cent of the original level after nine units of banked whole blood without any platelet transfusion. In our patient the platelet count after nine units of blood and six units of platelets was 102,000/mm$^3$, seven hours after the operation. PT and APTT were within normal limits, which are not the findings in dilutional thrombocytopenia.[9] It suggests that the patient had a low platelet count before the operation.

No explanation other than propylthiouracil-induced thrombocytopenia was identified, although the laboratory data were inadequate.

Forty-five days after the cervical laminectomy, the patient underwent a thyroidectomy without incident. Preoperatively he was treated with the same regimen as at the time of cervical laminectomy except that propylthiouracil was not being administered. His preoperative platelet count was 230,000/mm$^3$.

The overall haematological side effects from propylthiouracil reported to be 1.5 per cent.[10] The incidence of haemorrhagic diathesis due to propylthiouracil-related thrombocytopenia has not been reported. Certainly not all patients who have been treated with propylthiouracil bleed. There is no consistent relationship between the dosage of propylthiouracil and the occurrence of a coagulation defect.[10] It seems likely that excessive bleeding is dependent upon individual susceptibility rather than on the amount of the drug injected.

The haemorrhagic diathesis caused by propylthiouracil is not completely understood. Due to the decreasing use of propylthiouracil in the treatment of hyperthyroidism and the low incidence of a haemorrhagic complication associated with its use, this complication will be rarely encountered. Discontinuing the use of propylthiouracil on this patient was regarded to be advisable although perhaps not imperative. However when a patient taking propylthiouracil is admitted for operation and the past medical history and/or the physical examination suggest a bleeding tendency, a preoperative coagulation profile should be done. If a coagulation defect is found, it can be corrected by appropriate treatment. Propylthiouracil should be replaced by another therapeutic regime if possible before the scheduled operation. Vitamin $K_1$ (Mephyton) has been reported to be effective in correcting hypoprothrombinaemia.[1,2,4] However Vitamin $K_1$ has no known effect on platelets. In a surgical emergency perioperative platelet transfusion is the treatment for thrombocytopenia if excessive surgical bleeding is encountered.

In summary, a case of intraoperative bleeding due to propylthiouracil-induced thrombocytopenia is reported. The patient underwent another operation without incident 45 days after withdrawal of propylthiouracil. The value of preoperative coagulation studies in patients treated with propylthiouracil has been discussed.

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RÉSUMÉ

Les auteurs rapportent un cas d'hémorragie per-opératoire causée par une thrombocytémie déclenchée par le propylthiouracil. Un homme de 55 ans traité depuis deux mois au propylthiouracil a subis une laminectomie cervicale sans histoire à part le fait qu'il ait reçu sept unités de sang total, deux unités de culot globulaire, six unités de plaquettes et deux unités de plasma frais congelé pour une perte de sang évaluée à 5500 ml. Ce même malade subit une thyroïdectomie sans incident 45 jours après l'arrêt du propylthiouracil. Les tests de coagulation obtenus chez ce malade traité au propylthiouracil sont discutés.