eters were normal. Infectious and immunological investigations remained negative. Screening was negative for hepatitis B and C, HIV-1 and -2, and earlier positivities for hepatitis A, HVH, CMV, and EBV were found. Blood cultures remained negative. A trephine blood marrow biopsy showed absence of granulocyte and megakaryocyte series with a marked erythroid hypoplasia. All previous treatments were stopped and supportive therapy including antibiotics and platelet transfusions was undertaken. After 2 weeks, the WBC count was 3.1×10^9/L (with 0.5×10^9/L neutrophils), Hb 10.7 g/dl, and 25×10^9/L platelets. Hematological parameters reached the normal range 7 weeks after suppression of ticlopidine. A prophylaxis treatment of the neurological ischemic manifestations using acetylsalicyclic acid was started. No further hematological complication was mentioned during the next 6 months.

Patient 3

A 69-year-old man was recently admitted for a 1-week history of fatigue and amygdalitis. He had been taking atenolol and ticlopidine (500 mg/day) for 54 days, prescribed for a cerebro-vascular stroke and arterial hypertension. On admission, the spleen and the liver were not palpable. Investigations revealed WBC count 1×10^9/L (with 100% lymphocytes), Hb 8.7 g/dl, reticulocytes 8×10^9/L, and 57×10^9/L platelets. Biochemical parameters were normal. Screening was negative for hepatitis A and C and parvovirus. Earlier positivities for hepatitis B and CMV were found. A trephine bone marrow biopsy showed an aplastic marrow with only lymphoid lineage cells. Ticlopidine was initially stopped. Fever was noted during cytopenia, but blood cultures remained negative. Numerous purpuric skin lesions were found on the trunk. Treatment included supportive therapy with antibiotics and platelet transfusions, granulocyte–colony-stimulating factor (G-CSF) with a daily dose of 480 μg IV, and corticoids. Aspiration performed at day 43 showed a persistent hypoplastic bone marrow. At day 54, neutrophil count increased to $>0.5 \times 10^9$/L. At day 88, the peripheral blood counts were as follows: WBC count 5.8×10^9/L (with 3.9×10^9/L neutrophils), Hb 8.7 g/dl, reticulocytes 30×10^9/L, and 12×10^9/L platelets. Bone marrow aspiration remained hypocellular with an absence of megakaryocytes. The patient is currently maintained with platelet transfusion.

The myelotoxicity of ticlopidine has been known for >10 years [6], with an estimated incidence of severe neutropenia of around 1% [7,8]. The incidence of aplastic anemia is probably underestimated [1–5]. Our cases fill the criteria for drug-induced cytopenia and for the role of ticlopidine in occurrence. It has been reported that ticlopidine-induced aplasia would generally have a favorable outcome [5]. Nevertheless, one of our patients began medullary regeneration after >2 months. In agreement with Mataix et al. [1], we propose that this hematological toxicity of ticlopidine should be closely monitored, and that this risk be weighed when choosing ticlopidine as an antiaggregant drug rather than acetylsalicylic acid.

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Metronidazole: A Potential Therapeutic Agent in Paroxysmal Nocturnal Hemoglobinuria

To the Editor: In a patient with paroxysmal nocturnal hemoglobinuria (PNH), metronidazole therapy (1,200 mg/day) resulted in reduction of hemolysis and elevation of hemoglobin (Hb).

A 61-year-old man presented with easy fatiguability, progressive weakness, and exertional dyspnea in 1987. The hemoglobin (Hb) was 5.2 g/dl, platelets 54×10^9/L, total leukocyte count 4.8×10^9.L, and reticulocyte count 0.6%. Bone marrow biopsy was hypoplastic. Ham's acid and sugar water tests were negative. He was administered adroyd (120 mg/day) and prednisolone (40 mg/day). Seven months later, the reticulocyte count and Hb rose to 4.4% and 9.5 g/dl. Ham's and sugar water tests for PNH became positive, with 20.5% and 50% hemolysis, respectively. Fluorescent activated cell-sorter (FACS) analysis revealed the presence of two cell populations, with 48% cells negative for decay accelerating factor (DAF) Eighty percent of erythroid colonies were negative for acetylcholinesterase.

For the next 2 years, Hb was 9.5–14.5 g/dl, in response to either androgen/prednisolone therapy or a spontaneous remission [1]. Subsequently, Hb fluctuated (5.5–9.3 g/dl). Episodic hemoglobinuria appeared and persists which could be explained by growth advantage of PNH clone over the normal clone [2]. During the course of illness, diabetes mellitus was noted. Diamicron therapy (40–120 mg/d) led to a precipitous fall in Hb of ≤5.7 g/dl, requiring blood transfusions (2 units × 4 at 3-month interval). The hemolysis could have been intensified by the presence of sulfhydryl group in the drug [3]. Replacement with insulin improved the Hb level.

In January 1992, epigastric tenderness was noted. Metronidazole therapy (1,200 mg/day × 2 weeks was associated with a rise in Hb from 9 to 10 g/dl. A similar rise in Hb of ≥11 g/dl with metronidazole (1,200 mg/day × 4 weeks) was noted on five further occasions (Fig. 1). This was associated with a reduction in overt hemoglobinuria. After 2 weeks of withdrawal or reduction to 400 mg/day, the Hb level fell to 5.3 g/dl and 6.4 g/dl, respectively. A maintenance dose of 800 mg/day succeeded in maintaining the Hb at >11 g for prolonged periods, although low-grade hemolysis continued (plasma Hb ≤15 mg/dl). Physical and mental stress and infections increased the hemolysis in spite of the metronidazole. The Hb fluctuated at 7–12 g/l, but blood transfusions were not required.

In vitro incubation of metronidazole (50 μg/ml) with the patient's red cells or control sera did not alter the extent of hemolysis in the Ham's acid test with the patient's own or control sera. The serum complement (C3) levels in the patient were 94% and 90% with 400 mg and 1,200 mg metronidazole, respectively. The protective influence of metronidazole

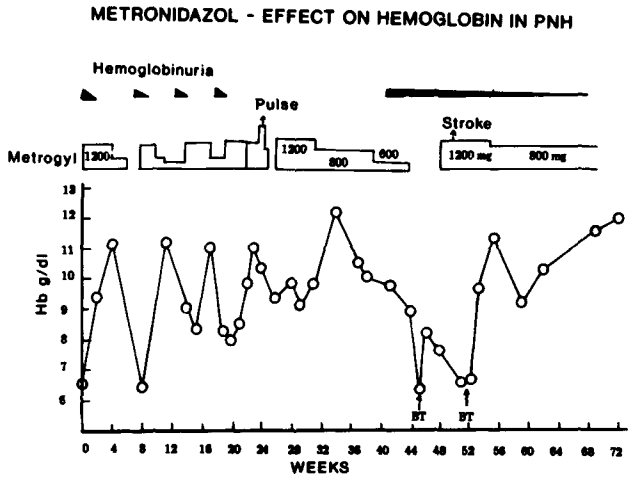

Fig. 1. Variation in hemoglobin levels and gross hemoglobinuria occurring with 1,200, 800, and 600 mg and the absence of metronidazole therapy. BT, blood transfusion.

was therefore not mediated via C3 nor by its combination with the red cell membrane. The possibility of its effect on the membrane attack complex of the complement, however, requires exploration [4].

Resident flora of the stool, with 1,200 and 400 mg metronidazole, revealed the growth of *Escherichia coli* (colony count of 10^{10} and 10^9/g, respectively), negating the effect of metronidazole via alteration of anaerobic flora of intestine unlike in chronic polyarthritis of unknown origin [5].

It is concluded that metronidazole may serve as a potential agent to alleviate severe anaemia and eliminate blood transfusion in PNH patients with active hemolysis associated with good bone marrow compensation.

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