Erythropoiesis Augmentation in a Jehovah's Witness with Gastrointestinal Bleeding

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INTRODUCTION

Because therapeutic options are limited, the treatment of anemia in a Jehovah's Witness patient with bleeding presents a dilemma for the clinician. This report describes erythropoiesis augmentation in a Jehovah's Witness with gastrointestinal bleeding.* The literature regarding the use of erythropoietin in gastrointestinal bleeding is also reviewed.

CASE REPORT

An 89-year-old female Jehovah's Witness presented to the emergency department with a 24-h history of melena. Her past medical history included depression, meningioma, chronic headaches, osteoarthritis, diverticulitis, stripping of varicose veins, left hip fracture, pyloroplasty for pyloric stenosis, restless legs, hysterectomy, appendectomy, and hemorrhoidectomy. Medications on admission were escitalopram 10 mg daily, ferrous fumarate 300 mg daily, and ibuprofen 200 mg 3 or 4 times daily as needed. She had no known allergies and weighed 43.2 kg.

On admission, the patient was afebrile, with blood pressure 116/67 mm Hg, heart rate 98 beats/minute, respiratory rate 18 breaths/minute, and oxygen saturation 84% on room air (a sample was not drawn for blood gas testing). She was alert and oriented. A head and neck examination revealed flat jugular venous pressure and dry mucous membranes. Cardiovascular examination revealed a soft-flow murmur at the lower sternal border; the results of the neurologic, respiratory, abdominal, and musculoskeletal examinations were unremarkable.

On admission, serum electrolytes, creatinine, glucose, activated partial thromboplastin time, international normalized ratio, troponin, and electrocardiography were normal. The following laboratory abnormalities were recorded: blood urea nitrogen 19.2 mmol/L (normal range 2.5–8.5 mmol/L), hemoglobin 46 g/L (normal range 120–160 g/L), and hematocrit 0.16 (normal range 0.36–0.48). The results of the anemia work-up were vitamin B_{12} 156 pmol/L (normal range 140–800 pmol/L), red cell folate 6748 nmol/L (normal range > 435 nmol/L), ferritin 35 mg/L (normal range 18–300 mg/L), and transferrin saturation 0.08 (normal range 0.20–0.55).

Fluid resuscitation was performed with 3 L of 0.9% sodium chloride, and oxygen was started at 3 L/min via nasal prongs. The patient was given an IV bolus dose of pantoprazole 80 mg, followed by an 8 mg/h infusion. Endoscopy revealed a large clean-based ulcer in the bulb of the duodenum and gastritis throughout the entire stomach. On day 2 the patient began empiric treatment for *Helicobacter pylori* with amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily. The patient reported that she felt very tired and weak. She was willing to try erythropoiesis augmentation with albumin-free erythropoietin 20 000 units (463 units/kg) SC daily, folic acid 5 mg PO daily, and vitamin B_{12} (cyancobalamin) 100 mg SC daily. The patient received iron sucrose 200 mg IV followed by 100 mg daily. After 3 days of IV pantoprazole therapy, she was stepped down to oral pantoprazole 80 mg twice daily. On day 5 the iron sucrose was discontinued. On day 7 the erythropoietin, folic acid, and cyancobalamin were discontinued, as the patient stated that she no longer felt tired or weak. On day 8 the amoxicillin and clarithromycin were discontinued. The patient remained in hospital for rehabilitation and was discharged on day 16 with a hemoglobin level

* Verbal consent was obtained from the patient to publish this case.

Table 1. Summary of Hemoglobin, Hematocrit, and Reticulocyte Index in a Jehovah's Witness Undergoing Erythropoiesis Augmentation

Variable	Day 1	Day 3	Day 5	Day 8	Day 12	Day 15	Day 35	Day 56
Hemoglobin (g/L)	46	49	56	73	73	75	94	121
Hematocrit	0.14	0.14	0.17	0.22	0.23	0.24	0.29	0.38
Reticulocytes (%)	ND	9	11.2	9.3	6.4	ND	ND	ND
Reticulocyte index	ND	2.8	4.2	4.6	3.3	ND	ND	ND

ND = not done.

of 75 g/L (Table 1). Her discharge medications were escitalopram 10 mg daily, pantoprazole 80 mg twice daily, and pramipexole 0.125 mg daily at bedtime.

DISCUSSION

There is very little literature documenting the use of erythropoietin in anemia secondary to gastrointestinal bleeding. A search of MEDLINE and the International Pharmaceutical Abstracts database (January 1966 to October 2007) with the Medical Subject Headings "Jehovah's Witness", "erythropoietin", and "hemorrhage" revealed 7 cases of erythropoietin use in Jehovah's Witnesses with this condition (Table 2).[1-5] Two additional cases were excluded because the duration of erythropoietin was not reported or there was no follow-up testing of hemoglobin.[6,7] There were no adverse events associated with erythropoietin therapy. One patient died secondary to abdominal sepsis.[1]

A small, randomized, prospective open-label study evaluated the use of erythropoietin in patients with acute ulcer bleeding or hemorrhagic gastritis.[8] The patients were randomly assigned to receive 100 mg ferric hydroxide polymaltose complex IM daily for 6 days (n = 15) or erythropoietin 20 000 units (300 units/kg) SC on days 0, 4, and 6 plus 100 mg ferric hydroxide polymaltose complex IM daily for 6 days (n = 15). The mean serum ferritin was 71 mg/L and transferrin saturation was 0.12. Hematocrit increased from 0.29 to 0.36 by day 14 in the erythropoietin plus iron arm and from 0.29 to 0.33 in the iron treatment arm. The authors suggested that this difference was equivalent to 1 unit of blood.

There are several reports of Jehovah's Witnesses who have survived severe anemia (hemoglobin less than 50 g/L) without receiving erythropoiesis augmentation. In one review, 27 patients with anemia secondary to trauma or surgery, ranging in age from 20 to 78 years (mean 44 years), survived remarkably low hemoglobin concentrations, ranging from 14 to 50 g/L (mean 34.9 g/L).[9] In many of these cases, prolonged neuromuscular blockade, hypothermia, deep sedation, or general anesthesia were instituted in an effort to reduce the patients' oxygen consumption and improve survival.

In another study, 32 healthy patients, ranging in age from 19 to 69 years (mean 27 years), underwent severe isovolemic anemia, which reduced the hemoglobin concentration from 124 to 50 g/L for 2.4 h, but they had no change in oxygen consumption or plasma lactate concentration.[10] Two young women experienced ST changes while on Holter monitor, related to body position or activity in one and to an increase in heart rate in the other; in both patients, the ST changes resolved without sequelae.[10]

In the case reported here, the patient had normal serum lactate (1.1 mmol/L; normal range 0.5–2.2 mmol/L) and oxygen saturation (84% on room air) at the time of admission. The low hemoglobin level might have affected the pulse oximetry reading, since a reduction in hemoglobin concentration causes the oxygen-carrying capacity of the blood to decline. In anemic hypoxia, the arterial partial pressure of oxygen is normal but, as a consequence of the reduction in hemoglobin concentration, the absolute quantity of oxygen transported per unit volume of blood is diminished.[11] In vitro and animal studies suggest that pulse oximetry readings may be affected by profoundly decreased hemoglobin concentration.[12] Low hemoglobin concentrations appear to cause falsely low readings when the oxygen saturation is below 80%; however, this effect is not clinically significant until the hemoglobin level is less than 50 g/L.[12]

Endogenous erythropoietin is secreted primarily by the kidney, with about 10% produced in the liver. The hormone is secreted in response to reductions in arterial and/or venous oxygen tension and tissue oxygenation in the kidney. The usual serum concentration of erythropoietin in healthy individuals with normal hematocrit is approximately 5–30 units/L. In anemia secondary to acute blood loss, the level may increase by up to 1000 times. Erythropoietin induces erythropoiesis by stimulating the proliferation and differentiation of erythroid precursors (burst-forming units-erythroid and colony-forming

Table 2. Summary of Reports of Erythropoietin Therapy in Jehovah's Witness Patients with Gastrointestinal Bleeding

Study	Age (yr)	Sex	Hemoglobin Nadir (g/L)	Erythropoietin Dosage	Duration (days)	Hemoglobin after Therapy (g/L)	Iron Route	B_{12} or Folic Acid
Walton and Macon[2]	50	M	35	250 units/kg SC daily for 2 doses, then 500 units/kg SC daily	30	76	PO*	None
Virchis et al.[3]	50	F	35	10 000 units SC daily for 1 dose, then 20 000 units SC daily for 4 doses, then 20 000 units SC every other day for 1 dose, then 10 000 units every other day for 3 doses†	27	128	IV‡	Folic acid 2 mg IV daily
Pousada et al.[4]	51	F	32	10 000 units SC 3 times weekly	28	116	PO*	Folic acid*
Schwenk and Blaustein[5]	66	F	48	20 000 units IV daily for 3 doses, then 6500 units IV every other day for 4 doses	12	90	PO*	B_{12} and folic acid*
Zaharia-Czeizler[6]	74	F	58	40 000 units SC daily for 1 dose, then 10 000 units SC daily	7	70	IV§	Folic acid 1 mg PO daily

*Dose, frequency, and duration not reported.
†Over the next 13 days the patient received an additional 4 doses of erythropoietin 10 000 units. SC.
‡Serum ferritin 2.5 mg/L; the patient also received iron dextran 200 mg IV daily for 5 days.
§Serum ferritin 15 mg/L; the patient received iron sucrose 500 mg daily for 6 doses.

units-erythroid). This results in increased production of erythroblasts and reticulocytes, the immature forms of erythrocytes. The hormone also stimulates the release of reticulocytes from the bone marrow and the synthesis of hemoglobin.[13]

The erythropoietic response to erythropoietin depends on the dose.[13,14] The drug usually induces erythropoiesis within 1 to 6 weeks, and increases in reticulocyte count may be seen within 10 days.[13] Erythropoietin doses of 600 units/kg daily were used in 2 cases in which anemia occurred secondary to surgery.[15,16] In one case, the hemoglobin increased from 19 to 63 g/L after 11 days of erythropoietin therapy.[15] In the second case, the hemoglobin increased from 35 to 93 g/L after 35 days of therapy.[16] Iron was given intravenously in both cases. Koenig and others[15] also administered folic acid and vitamin B_{12} intravenously (doses not reported). We chose a dose of 500 units/kg for the patient described here, rounding it down to 463 units/kg to allow use of the 20 000 unit prefilled erythropoietin syringe.

This case differs from many in the literature in that we measured baseline ferritin, transferrin saturation, red cell folate, and vitamin B_{12} levels, data that are seldom reported. Ferritin level above 100 mg/L and transferrin saturation greater than 0.20 are important factors used to determine a patient's response to erythropoietin. The normal iron content of the body is about 3 to 4 g, with about 2.5 g being found in hemoglobin.[17] IV administration of iron is the most effective and quickest way to replace iron stores, but in many of the previously reported cases, the iron was administered orally. Supplementation with folic acid and vitamin B_{12} has been suggested to enhance erythropoiesis.[18] However, many authors have not performed such supplementation or they have not reported the dose, route of administration, or duration of iron, folic acid, or vitamin B_{12} therapy, making it difficult for clinicians to apply such therapy in their practice. The current case suggests that an erythropoietin dose of 500 units/kg and supplementation with vitamin B_{12}, folic acid, and IV iron administration may allow an increase in hemoglobin concentration by 30 points within 7 days.

We stopped therapy when the patient reported feeling much better, at which point the hemoglobin concentration was greater than 70 g/L. This decision was consistent with the conclusions of a meta-analysis[19] of 10 randomized trials comparing restrictive transfusion

thresholds (hemoglobin between 70 and 100 g/L) with more liberal transfusion methods (hemoglobin greater than 100 g/L) in surgical, intensive care, and trauma patients; that study showed that mortality, rates of cardiac events, and length of hospital stay were unaffected with restricted transfusion, except for patients with myocardial infarction or unstable angina.

The routine use of erythropoiesis augmentation in patients presenting with gastrointestinal bleeding cannot be recommended, as there is no evidence of decreased mortality, decreased transfusion requirements, or shortened hospital stay. The cost to treat our patient with erythropoietin, iron sucrose, folic acid, and vitamin B_{12} was approximately $1900. Assuming that 1 unit of blood will raise the hemoglobin concentration 10 points, the patient would have required 3 units of blood (at a cost of about $1200) to increase hemoglobin to a similar level by transfusion alone. Upper gastrointestinal bleeding has a prevalence of about 170 cases per 100 000 adults per year, with an estimated total cost of US$750 million.[20] Using pharmacologic therapy to increase hemoglobin concentration could drastically increase the cost of treating this type of bleeding. However, erythropoiesis augmentation with erythropoietin 500 to 600 units/kg daily, intravenous iron, folic acid, and vitamin B_{12} is a reasonable option for patients who refuse blood transfusions. Therapy may be stopped when the hemoglobin concentration is greater then 70 g/L or the patient is asymptomatic.

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