Fatigue. We use a small battery of routine tests (Box 2). However, in the absence of a positive history or physical examination, laboratory tests are rarely helpful. Minor abnormalities in test results will be common, and most are unrelated to fatigue even in patients complaining of fatigue. Iron deficiency, even in the absence of anaemia, can cause fatigue, and treatment of the deficiency with iron appears to help in many such cases. Additional directed tests (e.g., HIV antibody testing) should be considered based on the patient’s history and the physical findings.

In the case of our patient with fatigue and elevated transaminase levels but without other typical features of celiac disease (steatorrhea, weight loss), the clinical index of suspicion (pretest probability) of celiac disease was estimated to be between 20% and 30%. Since the test for lgA antiendothymysial antibody has a high sensitivity and specificity (about 90% and 95% respectively), the positive likelihood ratio is about 30. By using the Fagan nomogram, we found that the positive predictive value (post-test probability) for this patient increased to about 90%.

The differential diagnosis of fatigue in primary care is very broad, but an organized approach to the patient as we have described can identify key conditions of concern efficiently and reduce the expensive workups for obscure conditions that this undifferentiated complaint can sometimes generate.

The drug: WinRho is a gamma globulin fraction of plasma containing antibodies to Rh(D) derived from blood donors. Donated plasma is stringently screened for known pathogens and then filtered to further reduce the risk of transmission of viruses such as hepatitis B and C, HIV and parvovirus.

WinRho is routinely given to Rh-negative women in their third trimester of pregnancy (28 weeks), postpartum (within 72 h) and after possible exposure to Rh-positive blood after pregnancy termination, amniocentesis or abdominal trauma, to prevent maternal Rh-antibody formation and hemolytic disease of the newborn in future pregnancies. WinRho is also used to treat ITP, an autoimmune disorder of increased splenic platelet destruction.

Pregnant women are treated with 120–300 µg of WinRho, administered intravenously or intramuscularly. Patients with ITP are given a much higher dose, generally 25–50 µg/kg intravenously. Common adverse effects, which often occur within minutes to days after the infusion, include headache, chills and fever, back pain and shaking. Serious but rare adverse effects have included acute respiratory distress syndrome, acute renal insufficiency, acute anemia and hemoglobinuria. The recent postmarketing case reports add DIC as another rare but potentially serious adverse effect, which likely starts as hemoglobinuria.

The 6 cases1 reported in the fall of 2005 were all submitted to the US Food and Drug Administration between 1999 and 2004. They involved 4 males and 2 females 12–85 years of age with ITP; all received doses of 48–75 µg/kg. Although most patients were discharged

References
1. Okkes IM, Oskam SK, Lamberts H. The probability of specific diagnoses for patients presenting with common symptoms to Dutch family physicians. J Fam Pract 2002;51:31-9.
2. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953-9.
3. Reid S, Chalder T, Cleare A, et al. Chronic fatigue syndrome. BMJ 2000;320:292-6.
4. Lane TJ, Matthews DA, Manu P. The low yield of physical examinations and laboratory investigations of patients with chronic fatigue. Am J Med Sci 1990;309:313-8.
5. Violani C, Devoto A, Lucidi F, et al. Validity of a short insomnia questionnaire: the SDQ. Brain Res Bull 2004;63:415-21.

Jacques Cornuz
Idris Guessous
Department of Community Medicine and Public Health
University Outpatient Clinic
Department of Medicine
University Hospital
Bernard Favrat
Department of Community Medicine and Public Health
University Outpatient Clinic
Lausanne, Switzerland

This article has been peer reviewed.

Competing interests: None declared.
feeling well, 4 experienced acute symptoms of hemoglobinemia or hemoglobinuria within 4 hours of receiving the drug (in the other 2 cases, the exact timing was not clear). All 5 patients were adults who died 3–10 days after being treated; their clinical and laboratory findings were consistent with DIC (e.g., increased prothrombin [PT] and partial thromboplastin times [PTT], fibrin degradation [FDP] or split products [FSP] and D-dimer; decreased fibrinogen level), but with no evident cause of DIC other than the drug treatment.

Cangene reports that a total of 9 cases of DIC have been reported internationally (one in Canada). For ITP patients, Cangene estimates the risk of intravascular hemolysis to be less than 1 in 1000; that of DIC, about 1 in 10 000. Patient age, sex and comorbid conditions do not appear to predict the adverse effect; neither do pretreatment renal function or hemoglobin levels, nor concomitant administration of other blood products. Some of the patients in whom DIC manifested had tolerated previous doses of the drug.

There are no known reports of intravascular hemolysis in pregnant women given WinRho.

**What to do:** Patients who receive WinRho should be warned of the risk of this rare but potentially fatal adverse event and advised to immediately report any “red flag” symptoms or signs (Box 1). Consideration should be given to close monitoring of patients with symptoms of acute hemoglobinemia or hemoglobinuria, anemia and renal insufficiency for signs of DIC. Appropriate laboratory tests include complete blood counts; PT and PTT; direct and indirect bilirubin; measurement of serum creatinine, urea, haptoglobin, lactate dehydrogenase, D-dimer and FDP/FSP; and urine dipstick and microscopic urinalysis.

It seems wise to advise pregnant patients of the theoretical risks of receiving a blood product.

Claire Kendall
Eric Wooltorton
CMAJ

REFERENCES

1. Gaines AR. Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(D) immune globulin intravenous administration for immune thrombocytopenic purpura. Blood 2005;106:1532-7.

2. Health Canada–endorsed important safety information on WinRho® SDF (Rh(D) immune globulin (human)). Available: www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/winrho_nth-aah_e.pdf (accessed 2006 Jan 31).

3. WinRho® SDF for injection [product monograph]. Winnipeg: Cangene Corp. Available: www.cangene.com/documents/winrho_monograph_e.pdf (accessed 2006 Jan 31).

All Health and Drug Alerts are posted online ahead of print and are available at www.cmaj.ca. This article was posted on Feb. 22, 2006.