HEALTH AND DRUG ALERT

WinRho and disseminated intravascular coagulopathy

Reason for posting: WinRho is a human blood product, Rh_0(D) immune globulin, widely used to treat immune thrombocytopenic purpura (ITP) and to prevent Rh alloimmunization in pregnant women who are Rh-negative. Recently, however, a case series[1] described 6 patients with ITP who were given WinRho who subsequently experienced severe hemolysis and disseminated intravascular coagulation (DIC); 5 of them died. The manufacturer, Cangene, has since issued "Dear Health Care Professional" letters in both Canada and the United States that warn of 9 international reports of this serious adverse effect.[2]

The drug: WinRho is a gamma globulin fraction of plasma containing antibodies to Rh_0(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.[3] The recent postmarketing case reports add DIC as another rare but potentially serious adverse effect, which likely starts as hemoglobinemia and hemoglobinuria.

The 6 cases[1] 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 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.

Box 1: Early indications of intravascular hemolysis

Symptoms

- Generalized weakness
- Lightheadedness
- Fever or chills
- Shortness of breath
- Chest pain
- Back pain
- Sudden weight gain
- Fluid retention
- Decreased urine output
- Discoloured urine
- Jaundice

Signs

- Dyspnea
- Edema
- Hemoglobinuria
- Hypotension
- Oliguria or anuria
- Pallor or jaundice
- Tachycardia
- Increased bruising
- Prolonged bleeding and clotting times*

*May be difficult to detect in cases of pre-existing immune thrombocytopenic purpura.

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

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REFERENCES

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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.

DOI:10.1503/cmaj.060201