Cefotetan-induced immune hemolytic anemia following prophylaxis for cesarean delivery

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Second- and third-generation cephalosporins, notably cefotetan, are increasingly implicated in severe, sometimes fatal immune-mediated hemolytic anemia. We describe a 26-year-old woman who developed severe hemolytic anemia 2 weeks after receiving a single prophylactic dose of cefotetan during cesarean delivery. The patient's DAT was weakly reactive for IgG and her serum reacted with cefotetan-coated RBCs. The antibody had a titer of 4096 by antiglobulin testing. The patient required treatment with two units of PRBCs and experienced gradual resolution of hemolysis. Our case emphasizes the need for increased awareness of delayed onset hemolytic anemia following prophylactic use of cefotetan. ***Immunohematology*** **2004;20:63–66.**

Key Words: cefotetan, cesarean delivery, DAT, drug-induced hemolytic anemia, immune hemolytic anemia

Cefotetan is a second-generation cephalosporin active against gram-positive and gram-negative aerobic and anaerobic bacteria.[1] Because of its broad-spectrum antibacterial activity, cefotetan is a popular choice for antimicrobial prophylaxis during surgical and obstetric procedures.[2] A single dose is commonly administered after cesarean deliveries to reduce the incidence of postpartum endomyometritis.[3] Although short-term prophylaxis with cefotetan is thought to carry minimal adverse effects, several cases of severe hemolytic anemia have been associated with the use of this drug, some of which have been fatal.[4–20] We present a case of severe hemolytic anemia 2 weeks following cefotetan prophylaxis for cesarean delivery.

Case Report

A healthy 26-year-old woman underwent an uncomplicated cesarean delivery. Perioperatively, a single prophylactic dose of cefotetan (1.0 g) was administered intravenously. Her hospital course was uneventful and she was discharged home in stable condition. Routine laboratory work-up upon discharge, including a complete blood count, was within normal limits.

Two weeks following delivery, the patient returned to the hospital complaining of fatigue and shortness of breath. She had a significant anemia with Hct of 14.8 percent. Serum LDH was 750 IU/L; total bilirubin was 3.5 mg/dL, and direct bilirubin was 1.0 mg/dL. The reticulocyte count was 15% (corrected 5.3%). A peripheral blood smear revealed marked polychromasia and nucleated RBCs. Other laboratory studies, including platelet count, PT, aPTT, and serum fibrinogen, were within normal limits. Serum blood urea nitrogen, creatinine, haptoglobin, and liver function studies were also normal. Urine, stool, and blood cultures demonstrated no growth. The patient was transfused with two units of PRBCs and experienced gradual resolution of hemolytic anemia. She was discharged home in stable condition.

Materials and Methods

Routine serologic techniques were used. Drug studies were performed as described by Arndt et al.[19] A 40 mg/mL solution of cefotetan was prepared in PBS (pH 7.1). One aliquot of washed PRBCs was incubated with 10 volumes of the drug solution for 2 hours at 37°C. The RBCs were washed × 3 and resuspended to a 5% solution. The patient's serum was diluted 1 in 20. Normal serum, tested in parallel, was also diluted 1 in 20. Two drops of the diluted serum were incubated with one drop of untreated or cefotetan-treated RBCs for 1 hour at 37°C. Tests were read after a brief centrifugation and after IAT. Tests for reactivity by the so-called immune complex mechanism were as described.[19] Titration studies were performed using doubling dilutions of serum. An eluate was prepared using the patient's RBCs and the Elu-kit II (Gamma Biologicals, Norcross, GA). Additional samples were submitted for serologic investigation of drug-induced hemolytic anemia.

Results

No unexpected antibodies were detected using antiglobulin techniques including albumin, LISS, PEG, and MTS IgG gel cards (Micro Typing Systems, Pompano Beach, FL). An acid eluate was nonreactive with all cells tested by LISS, PEG antiglobulin testing, and IgG gel card. The DAT was weakly positive using anti-IgG and negative using anti-C3. There was insufficient eluate to test against cefotetan-coated RBCs. Further testing revealed anti-cefotetan in the patient's serum reacting with cefotetan-coated RBCs. The antibody was strongly reactive and had a titer of 4096 by saline IAT. Test results were negative with untreated RBCs when a 1mg/mL solution of cefotetan was added to the serum (Table 1).

Table 1. Serologic characteristics of drug-induced hemolytic anemia

	Drug adsorption[23]	Neoantigen formation[23]	Autoantibody[23]	Patient
DAT				
Polyspecific	+	+	+	+
IgG	+	Usually –	+	+
C3	Usually –	+	Usually –	–
Serum Antibody				
Routine	–	–	+/–	–
Soluble drug	–	+	+/–	–
Drug treated RBCs	+	–	+/–	+
RBC Eluate				
Routine	–	–	+	–
Soluble drug	–	–	+	NT*
Drug treated RBCs	+	–	+	NT*

*Not tested

Discussion

Cefotetan is presently the most common cause of drug-induced hemolytic anemia.[19] A recent search of the FDA's spontaneous reporting system and the World Health Organization's database revealed 85 cases of hemolytic anemia since the introduction of cefotetan in 1985.[20] Prior to this review, case and case series reports involving 60 patients with hemolytic anemia associated with this drug had been documented.[4–19]

Immune hemolytic anemia (IHA) secondary to sensitization with cefotetan can result from several types of interactions between the drug, antibodies, and RBC membrane components. These include drug adsorption onto the RBCs, neoantigen ("immune complex") formation, and induction of autoantibodies.[19,21–23] IHA secondary to drug adsorption occurs when IgG antibodies directed against the drug interact with RBCs to which the drug is strongly bound. The in vivo IgG-coated RBCs are then destroyed in the reticuloendothelial system by extravascular hemolysis. IHA due to neoantigen formation is thought to occur when a drug binds weakly to normal RBCs and the immune system perceives the drug-RBC complex as foreign. Autoantibodies are directed against membrane components and do not require the drug for subsequent reactivity. These mechanisms can be distinguished on the basis of serologic reactions of the serum and the eluate (Table 1). The proposed mechanisms are not mutually exclusive and may occur in combination.[21–23] In the majority of IHA cases due to cefotetan, both the drug adsorption and the "immune complex" mechanisms have been implicated.[19]

Our patient had clinical evidence of extravascular hemolysis, characterized by slowly decreasing Hct, absence of hemoglobinuria, and normal serum haptoglobin. Immunohematology work-up confirmed the presence of cefotetan-dependant antibodies. The DAT was weakly positive for IgG. The patient's serum reacted with cefotetan-treated RBCs, supporting the diagnosis of cefotetan-induced hemolytic anemia by the drug adsorption mechanism. The antibody titer was 4096 by saline IAT. This is in agreement with other reports in the literature, as cefotetan antibodies have been shown to be of high titer when compared with other drug antibodies.[19]

IHA has been recognized in obstetric patients receiving cefotetan prophylaxis during cesarean delivery. Gallagher et al.[4] published a case of a 27-year-old woman who developed severe hemolytic anemia 10 days after cefotetan prophylaxis during cesarean section. Mechanism of hemolysis involved both drug adsorption and "immune complex" formation. The patient eventually recovered after receiving steroids and four units of PRBCs. Garratty et al.[17] described six obstetric patients receiving cefotetan prophylaxis for cesarean section. Hemolytic anemia, requiring two to seven PRBC transfusions, developed 9 to 14 days after antibiotic prophylaxis. The drug adsorption and "immune complex" mechanisms were implicated in all their patients. Naylor et al.[18] reported three additional cases of cefotetan-induced hemolytic anemia following cesarean delivery. Hemolytic anemia occurred 9 to 12 days after administration of cefotetan and was confirmed in all patients by the drug adsorption, "immune complex," or both mechanisms. One patient was treated with steroids, while another was transfused with four units of PRBCs. The third patient received

steroids and four units of PRBCs. More recently, Arndt[16] reported a 31-year-old woman who developed hemolytic anemia 6 days after receiving two doses of cefotetan for cesarean delivery. The patient required transfusion with two units of PRBCs. Drug adsorption, autoantibody formation, and "immune complex" mechanisms were implicated. The patient had a previous history of hemolytic anemia occurring after cefotetan prophylaxis for cesarean delivery. The author concluded that in retrospect, the earlier episode of hemolysis may have also been due to an antibody to cefotetan.

The diagnosis of cefotetan-induced hemolytic anemia following prophylaxis for surgical procedures may not always be obvious. An autoantibody (drug-independent antibody) in a patient's serum or eluate may lead to an erroneous diagnosis of autoimmune hemolytic anemia. Likewise, blood transfusion during surgery may initially raise suspicion of a delayed hemolytic reaction if the DAT is positive. Women are predisposed to anemia during normal pregnancy, because of a disproportionately increased plasma volume compared with the RBC mass.[24] Unless excessive blood loss occurs during delivery, the Hct generally increases in the immediate postpartum period. When anemia occurs unexpectedly in the postpartum period, if associated with the use of antibiotics, immune-mediated hemolytic anemia should be considered and investigated before more cefotetan is given. In certain instances, the drug antibody can be easily detected with minimal drug investigation studies, such as the use of serum and titration studies as demonstrated in our patient, while in others, a more extensive drug study with the use of enzyme-treated RBCs may be necessary.

Hemolytic anemia associated with cefotetan prophylaxis usually becomes apparent about 7 to 10 days after administration.[19] A single dose can result in severe hemolytic anemia. The DAT can range from weakly reactive to a strong (4+) reaction. In most cases, the anemia resolves gradually, although the positive DAT may persist for several weeks. Transfusion support with PRBCs is indicated in the majority of patients.[19]

Because there is no universally accepted treatment for cefotetan-induced IHA, the main goal is prevention. Second- and third-generation cephalosporins have been frequently associated with severe hemolytic anemia when compared with first-generation cephalosporins.[19] Indeed, there are only five well-documented cases of hemolytic anemia attributed to first-generation cephalosporins. Double-blind controlled trials in obstetric and gynecologic surgery have demonstrated no clear advantage of the more expensive broad-spectrum agents over the first-generation cephalosporins. For prophylaxis of infection in patients undergoing obstetric surgery, cefazolin, a first-generation cephalosporin, is associated with fewer cases of IHA and may be preferable to cefotetan.[25]

Our case, in addition to others reported in the literature, confirms the importance of considering drug-induced hemolytic anemia whenever an obstetric patient develops unexpected anemia following antibiotic prophylaxis. This is especially true in cases when the patient returns to the hospital 1 to 2 weeks after receiving the prophylactic cefotetan. It is important, once the diagnosis is established, that the patient's physician be informed and that the patient be counseled not to receive cefotetan again.

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