Ceftriaxone-induced hemolytic anemia is a rare and often life-threatening complication of ceftriaxone use, particularly in patients with an underlying immunodeficiency or sickle cell disease. Induced hemolysis is associated with complement activation, resulting in rapid intravascular hemolysis in susceptible individuals leading to shock, multiorgan dysfunction, and often death. These events are more pronounced in pediatric patients, where the average time to hemolysis is 27 minutes postinfusion and over half more pronounced in pediatric patients, where the average time to hemolysis is 27 minutes postinfusion and over half of these events prove fatal. We report here the case of a 6-year-old female with sickle cell disease who survived a brisk and profound hemolytic reaction, resulting in hemoglobin of 0.4 g/dL, after ceftriaxone infusion. Ongoing hemolysis was abrogated with aggressive supportive care, but the patient suffered extensive neurologic sequelae as a result of the event. Serologic testing confirmed the presence of ceftriaxone antibodies.

**Key Words:** ceftriaxone, hemolysis, sickle cell disease, cerebral ischemia

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Severe Ceftriaxone-induced Hemolysis Complicated by Diffuse Cerebral Ischemia in a Child With Sickle Cell Disease

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over the next 12 hours received plasmapheresis followed by IV immunoglobulin 1 g/kg. Subsequent hematocrit was stable. She did not receive any further ceftriaxone and instead was placed on vancomycin and cefotaxime for broad-spectrum antimicrobial prophylaxis. Magnetic resonance imaging carried out 3 days after the event demonstrated an acute ischemic cerebral injury. Neurologically, she was initially responsive only to noxious stimuli. She was extubated 3 days after the event, and over the next 4 days showed some improvement in her neurologic function marked by her recognition of family members and the ability to follow a few simple commands. Upon transfer out of the ICU to the neurorehabilitation unit, she was awake, moving extremities spontaneously, and following several basic commands.

Four weeks after the event, the patient’s serum was sent to the American Red Cross Reference Laboratory in Los Angeles for analysis. DAT revealed weak reactivity with anti-IgG and anti-C3, and no reactivity with anti-IgM and anti-IgA. Testing for ceftriaxone antibodies demonstrated that untreated RBCs, in the presence of the patient’s serum and ceftriaxone, were strongly agglutinated after the 37°C incubation and weakly reactive by the antiglobulin test. Enzyme-treated RBCs, in the presence of the patient’s serum and ceftriaxone, were moderately hemolyzed and agglutinated after the 37°C incubation, and strongly reactive by the antiglobulin test. This testing therefore confirmed the presence of an antibody to ceftriaxone. Summary of the patient’s hospital course and serologic testing results is shown in Figure 1.

The patient stayed in the hospital for an additional 6 weeks to receive intensive neurorehabilitation, and she continued to show improvement in her speech and motor functions with ongoing physical and occupational therapies. Given the fact that individuals with sickle cell disease have a reported risk of up to 90% for repeated strokes after an initial event and this risk may be reduced to nearly 10% with regular exchange transfusions; she was offered a regimen of scheduled exchange transfusions to optimize her chances for neurologic recovery.

**DISCUSSION**

Many of the cephalosporins have been implicated in immune hemolytic anemia, most with only a few cases reported. Cefotetan and ceftriaxone, however, have been more extensively reported and studied among this group of antibiotics as a cause of hemolysis. There are 15 prior reports of pediatric ceftriaxone-induced immune hemolysis in the literature to date, with 53% of these cases resulting in death. Most of these children had an underlying immunodeficiency and 5 had sickle cell disease. In each case, there was a history of prior ceftriaxone exposure. The ceftriaxone-induced hemolysis tends to be more acute and severe in children as compared with adults, with an onset within 30 minutes in the majority of cases. Back pain, anemia, and shock are common presenting symptoms, with complement activation causing an abrupt intravascular hemolysis and hematuria. Successful treatment of ceftriaxone-induced hemolysis depends upon rapid identification of the situation, supportive care including IV fluid and blood product administration, and immediate cessation of ceftriaxone therapy. Of note, ceftriaxone-induced hemolysis presents in a very similar way to acute posttransfusion reaction and therefore, ceftriaxone should be considered as the possible offender in any such case involving its use. In this case, the patient survived despite of an Hgb of 0.4 g/dL, albeit with severe neurologic damage. To our knowledge, this is the lowest recorded Hgb in a surviving individual.

In general, drug-induced hemolysis may occur in either a drug-dependent or drug-independent manner. A proposed unifying theory of drug-induced antibody reactions postulates that antibodies may be made to the drug (such as in penicillin induced hemolytic anemia), the RBC membrane alone (as in methyldopa-induced hemolytic anemia), or to the drug-RBC complex (producing an in-vitro “immune complex” reaction). Unlike the other cephalosporins, which may produce antibodies by all 3 mechanisms, ceftriaxone induces only antibodies detected by the in-vitro “immune-complex” method. This detection requires the presence of patient serum, drug, and RBCs. Occasionally, positive reactions are elicited only by using enzyme-treated RBCs or metabolites of the drug.
and as demonstrated in this case, the DAT is positive for complement and IgG, and is without detectable IgA or IgM.1

In a study of 64 pediatric patients with human immunodeficiency virus (HIV) or sickle cell disease (45 HIV and 19 significant contagious diseases), Quillen and colleagues17 found the prevalence of ceftriaxone antibody was 12.5% (8 of 64). Two of these 8 patients had clinically evident hemolysis (both with HIV) and one of them suffered a fatal hemolytic event within minutes of receiving ceftriaxone. Six of the 8 patients in the analysis had confirmed prior exposure to ceftriaxone and exposure was unknown for the remaining 2. The results of this study suggest that detectable ceftriaxone antibody, although present in those individuals with obvious hemolysis, is not always associated with severe reactions. Given the frequency at which ceftriaxone is used for broad-spectrum prophylaxis, the prevalence and clinical significance of ceftriaxone antibodies awaits larger studies of at-risk populations. Further, it is presently unclear whether the association of ceftriaxone-induced hemolytic anemia with individuals with immune deficiencies or sickle cell disease is a result of simply having greater exposure to the drug or there are other predisposing factors for immune-mediated hemolysis associated with these conditions.

In any case, the risk versus benefit of routine use of ceftriaxone for broad-spectrum antimicrobial prophylaxis should be carefully considered. Despite the convenience of 24-hour dosing, the often-fatal outcome of ceftriaxone-induced hemolysis should cause health care providers to consider possible alternatives. After this event, cefotaxime 50 mg/kg IV every 8 hours has become the broad-spectrum antimicrobial agent of choice in our sickle cell population. Care should be taken to avoid ceftriaxone in individuals with previously identified antibodies, and the presence of ceftriaxone antibodies should be considered in cases of hemolysis in which the drug was used, despite a history of uncomplicated prior exposure. The case presented here provides a classic example of the rapidity and severity of hemolysis that occurs in ceftriaxone-induced hemolytic anemia.

REFERENCES


