

CORRESPONDENCE

Adverse drug reactions during ceftriaxone treatment can cause severe hemolysis

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To the Editor,

Case report

Adverse drug reactions can lead to hemolysis if left untreated. Here, we report such a case. A 4-yr-old girl was administered intravenous ceftriaxone (1.5 g/day) to treat acute laryngotracheal bronchitis. During her therapy, she experienced adverse drug reactions three times, leading to hypotension, fever, and ultimately hemolysis. 5 days after the initiation of ceftriaxone treatment, the patient began exhibiting symptoms, namely weakness, inability to stand, sickly pallor, and minor abdominal discomfort. Her blood pressure (BP) was low at 70/40 mmHg, and her spleen was not palpable upon physical examination. Thus, ceftriaxone was halted. She received oxygen and was infused with physiologic saline. Within 30 min, her condition was improved, as evidenced by an increased BP to 110/60 mmHg. Approximately 10 h after ceftriaxone cessation, the girl manifested transient urticaria, which disappeared following chlorphenamine treatment. She also reported transient abdominal pain and exhibited an increase in body temperature (up to 38.4°C), which eventually returned to normal. On the sixth day, some of these symptoms, namely inability to stand, weakness, and sickly pallor, reemerged, when ceftriaxone treatment was reinitiated. Although her BP remained stable at 100/40 mmHg, her spleen was still not palpable. Her hemoglobin (Hb) level was reduced from 133 g/l at the start of ceftriaxone treatment to 48 g/l. However, her liver function was normal. Because a urine test indicated hemoglobinuria, a direct antiglobulin test (DAT) was positive, and a blood smear revealed ruptured erythrocytes, the patient was diagnosed with drug-induced immune hemolytic anemia (DIIHA). Therefore, ceftriaxone was halted. She was administered dexamethasone to suppress allergic reactions and sodium bicarbonate to protect renal function. On the seventh day, her spleen could be felt 1 cm below the arch of her ribs and her Hb level was higher at 83 g/l. Evidence of hemolysis was further observed in tests of liver function, which demonstrated that her levels of total bilirubin (TBIL) and indirect bilirubin (IBIL) were 42.4 μ M and 36.4 μ M, respectively. Renal function tests showed that her level of urinary albumin was 123 mg/l, urinary transferrin was 28.6 mg/l, urinary α 1-microglobulin was 49 mg/l, and urinary β 2-microglobulin was 0.456 μ g/ml. As a result, she began receiving methylprednisolone sodium succinate and sodium bicarbonate. On the ninth day, her urine test produced normal results. By the tenth day, her Hb, TBIL, and IBIL levels were 86 g/l, 17.8 μ M, and 13.9 μ M, respectively. On the thirteenth day, her Hb was measured at 95 g/l but her urine, renal, and liver test results were normal. In addition, her spleen was not palpable.

Therefore, the patient was discharged from the hospital on the thirteenth day.

Discussion

This patient experienced adverse drug reactions three times while undergoing ceftriaxone therapy to treat acute laryngotracheal bronchitis. The first instance resulted in hypotension, while the second and third instances caused fever and hemolysis, respectively. Note that on the fifth day, hemolysis was not observed (on the sixth day TBIL, 15.5 μ M; IBIL, 11.4 μ M); and the fever occurred 10 h after ceftriaxone cessation. These results suggest that adverse drug reactions continued despite cessation of ceftriaxone therapy. Interestingly, when ceftriaxone treatment was reinitiated on the sixth day, hemolysis was observed. The severity of the adverse drug reactions increased following administration of the drug. Moreover, she exhibited an enlarged spleen after hemolysis, suggesting the presence of extravascular hemolysis. A multitude of drug reactions were manifested with these drug therapies in this patient; however, we focus only on DIIHA in this article.

DIIHA is a rare condition, and the underlying mechanisms that lead to its manifestation remain controversial. One potential mechanism involves the covalent binding of ceftriaxone-induced antibodies (typically IgG isotypes) to proteins on the membrane of red blood cells (RBCs). Such binding results in the elimination of RBCs by macrophages, and possibly the complement system, in the extravascular space (1). Studies have shown that drug-dependent antibodies (DDABs) can only be detected in the presence of drug, while drug-independent antibodies (DIABs) can be detected *in vitro* in the absence of drug. Cefotetan, ceftriaxone, and piperacillin are frequent causes of DDAB production. On the other hand, fludarabine, methyl dopa, and β -lactamase inhibitors are frequent causes of DIAB production. DDABs typically demonstrate a positive DAT result and negative elution. Hemolysis usually appears within 2 wk after initiation of the drug treatment. The only effective response against DDAB-mediated DIIHA is cessation of the drug that induced DDAB production. To date, there is no compelling evidence showing that steroids are effective in treating DDAB-mediated DIIHA; thus, they should not be used to treat DIIHA (2). This observation is especially important for infected or immunosuppressed patients (We made a mistake to use steroids in this case). In DIAB-mediated DIIHA, the drug affects the immune system and causes production of RBC autoantibodies. This effect is identical to warm autoimmune hemolytic anemia (WAIHA). In fact, DIAB-mediated DIIHA cannot be distinguished from WAIHA in *in vitro* testing because both show a positive

DAT and positive elution. Only hematologic improvement following the drug cessation can confirm the diagnosis of DIABs DIIHA. Unlike DABB-mediated DIIHA, steroids can be used to treat this condition (2).

Two other mechanisms for DIIHA pathogenesis have been proposed. One involves the generation of antibodies against membrane-drug complexes present on the RBC surface (1). These complexes subsequently induce the generation of antibodies (IgG or IgM) that activate complement and lead to acute intravascular hemolysis and sometimes renal failure. The other possible mechanism involves drug-induced non-immune protein adsorption. In 1971, Spath et al. (3) found that cephalothin-treated RBCs adsorbed IgG, albumin, C3, and fibrinogen among other molecules. This drug promoted the non-immunologic adsorption of proteins onto the RBC membrane. Monocyte monolayer assays using such coated RBCs yielded positive results, suggesting that macrophages would likely respond to these RBCs to cause hemolysis (1).

The first case of ceftriaxone-related DIIHA was reported in 1991 by Garratty et al. (4). Since then, many instances of this condition have been reported. Boggs and colleagues published that 63% (of 27 patients) were younger than 18 yr of age and that the mortality rate was 47% among the pediatric group (5). Furthermore, at least eight children experienced acute renal failure, of which five did not survive. Garratty et al. (1) reported that 40% (of 15 children) developed hemolysis less

than 1 h after receiving ceftriaxone treatment. In a review of 11 cases of ceftriaxone-related DIIHA, the DAT result was reported as positive along with the presence of anti-IgG, anti-C3d, or both in most cases (6). Ceftriaxone antibodies were also detected in the serum (1).

Based on these data, it is clear that ceftriaxone-induced hemolytic anemia in children may be severe and fatal. Once this condition is suspected, ceftriaxone treatment should be stopped even if the symptoms appear minor and inconsequential. Hematologic recovery commonly occurs within 2 wk, but the DAT result may remain positive for weeks or months thereafter. As our case showed, continued ceftriaxone treatment may exacerbate DIIHA. Confirmatory tests should be performed. However, steroids should not be administered.

Conclusion

In conclusion, ceftriaxone-induced hemolytic anemia is a rare yet severe condition in children. Once observed, administration of the drug suspected to induce DIIHA should be ceased and steroid treatment should be avoided.

Wei Liu¹ & Dongyan Yu²

¹Weihai Municipal Hospital, Weihai, Shandong, 264200, China;

²Weihai Jingqu Hospital, Weihai, Shandong, 264205, China

E-mail: yudongyan@outlook.com

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