Cephalosporin Side Chain Idiosyncrasies: A Case Report of Ceftriaxone-Induced Agranulocytosis and Review of Literature

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Keywords. agranulocytosis/chemically induced; ceftriaxone; cephalosporin; drug adverse effect; neutropenia/chemically induced.

Drug-induced neutropenia is characterized by a sharp decrease in the absolute neutrophil count (ANC) to <500/mm^3; agranulocytosis is said to be present once the granulocyte count reaches zero. Although associated with a large variety of drugs, this adverse effect is rare, occurring in 2.4–15.4 cases per million courses of therapy [1]. Because of its efficacy and relative safety, ceftriaxone is commonly used for treating a broad range of serious infections [2]. In this report, we describe a patient who developed agranulocytosis during treatment with ceftriaxone and recovered after treatment was changed to cefepime, and we review previously reported cases of ceftriaxone-induced agranulocytosis.

METHODS

We searched PubMed, Scopus, and the Cochrane Library for ceftriaxone-induced agranulocytosis, using "agranulocytosis" or "neutropenia" and "drug-induced" or "ceftriaxone" or "cephalosporin." Reports from all years and all languages were included. Additional reports were identified using citations in all retrieved papers to identify cases that were not found in the initial search. Articles that reported a case of ceftriaxone-induced acute agranulocytosis or neutropenia were included. We excluded articles if individual patient details were not reported or if the ANC nadir was not stated to be <500/mm^3. The relationship between neutropenia and ceftriaxone treatment was assessed for each case using the Naranjo Adverse Reaction algorithm [3].

CASE REPORT

A 49-year-old homeless polysubstance abuser was admitted for severe lower back pain that began 3 weeks earlier, after self-extraction of an infected tooth. Upon presentation, laboratory results were remarkable for leukocytosis (15×10^9/L) with an ANC of 12 690/mm^3. Magnetic resonance imaging (MRI) revealed vertebral osteomyelitis, phlegmon, and an epidural abscess (L4). Four blood cultures yielded *Streptococcus intermedius,* and a 6-week course of intravenous ceftriaxone was prescribed, initially at 1 g every 12 hours, which, after 4 days, was increased to 2 g every 12 hours. At the start of treatment, his serum creatinine was 0.8 mg/dL and remained stable throughout.

On day 25 of ceftriaxone therapy, a routine complete blood count documented an ANC of 480/mm^3, down from 4435/mm^3 12 days previously. His hemoglobin and hematocrit and platelet counts remained unchanged from his baseline complete blood count. The following day, he developed a sudden fever to 103.3 F. There were no new clinical signs or symptoms, including rash, suggesting an alternative cause. The peripherally inserted central catheter line site was clean, without purulence, and was removed. Because of concern for neutropenic fever, ceftriaxone was discontinued, and treatment was broadened to cefepime 2 g every 8 hours and vancomycin 2 g every 12 hours. The ANC fell to 0 on day 28. No new source of infection was found; all cultures were subsequently negative, and additional laboratory results were otherwise unremarkable. The patient's other medications at time of neutropenia were not associated with prior reports of agranulocytosis [4], and ceftriaxone was the only medication discontinued. Given the timing and the prior literature reports on beta lactamase-

Received 17 November 2014; accepted 14 January 2015.

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Open Forum Infectious Diseases

DOI: 10.1093/ofid/ofv007

Table 1. A Comparison of Clinical Characteristics Among Reported Ceftriaxone-Induced Agranulocytosis Cases

Ref	Indication	Daily Dosage, Duration/ Total Dose	Time to Neutropenia (Days)[a]	ANC Nadir (Cells/mm^3)	Time to Recovery (Days)[b]	Complications	Comments
[5]	Bacteremia (*Streptococcus pneumococcus*)	2 g, 11 days; 1 g, 14 days/ 36 g	NR	18	7	None	
[6]	Endocarditis (*Streptococcus sanguis*)	2 g, 37 days/74 g	42	62	4	Fever (100.7F)	Received cefazolin 24 g over 7 days prior to ceftriaxone
[7]	Lung abscess (*Pseudomonas stutzeri*)	2 g, 14 days/28 g	14	NR	18	None	Received cefotaxime 3 g daily for 6 days prior to ceftriaxone
[8]	Seronegative Lyme disease	4 g, 21 days/84 g	25	345	NR	*Clostridium difficile* colitis, fever (103.1F), rash, hepatitis	
[9]	Liver abscess (*Streptococcus milleri*)	1 g, 32 days/32 g	40	0	5	Fever	
[9]	Liver abscess (*S milleri*)	2 g, 7 days; 1 g, 42 days/ 56 g	49	360	7	None	
[10]	Endocarditis (*S sanguis*)	2 g, 27 days/54 g	27	30	NR	None	Received penicillin G 18 million units daily for 17 days and developed fever prior to ceftriaxone
[11]	Staghorn calculus pyelonephritis	1 g, 18 days/18 g	18	170	5	Fever, thrombocytopenia	
[12]	Endocarditis (*Streptococcus bovis*)	2 g, 18 days/36 g	18	242	3	Generalized seizure	Received amoxicillin for 12 days and developed rash prior to ceftriaxone Treated with G-CSF
[13]	Endocarditis (*Streptococcus mutans*)	2 g, 5 days/10 g	5	75	5	Fever (101.3F), thrombocytopenia, anemia	Received penicillin 20 million units daily for 31 days and developed hemorrhagic cystitis and eosinophilia prior to ceftriaxone
[14]	Endocarditis (*Cardiobacterium hominis*)	2 g, 21 days/42 g	21	20	10	Gingivastomatitis, submandibular abscess	History of penicillin-induced agranulocytosis
[15]	Pyelonephritis	2 g, 15 days; suspended 3 wks; 2 g, 5 days/40 g	5 (from 2nd course)	<51	N/A (died)	Fever (102.3F), eosinophilia, septic shock, death	Treated with G-CSF
[16]	Lyme disease	2 g, 16 days/32 g	14	0	1	Pharyngeal erythema	Treated with G-CSF
	Osteomyelitis (*Streptococcus intermedius*)	2 g, 4 days; 4 g, 22 days/ 96 g	25	0	7	Fever (103.3F)	

Abbreviations: ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; N/A, not applicable; NR, not reported; Ref, reference.

[a] Calculated from start of ceftriaxone dose to recognition of neutropenia (<500/mm^3).

[b] Recovery defined as ANC returning to normal levels (>1500/mm^3) after cessation and/or alternative therapy.

induced agranulocytosis, ceftriaxone was believed to be the most likely cause. Over the next few days, his white blood cell count began to rise, and his fever resolved. On day 32, 1 week after discontinuation of ceftriaxone and while he was receiving cefepime, the patient's ANC had returned to normal levels (2024/mm^3). Repeat MRI of the spine revealed improved L4–L5 osteomyelitis. The patient recovered clinically and was discharged with oral clindamycin 450 mg 3 times daily for 2 weeks to complete 6 weeks of therapy.

DISCUSSION

Our patient developed agranulocytosis during prolonged treatment with 4 g of ceftriaxone daily, yet he recovered while on cefepime. Despite the widespread use of ceftriaxone, there have been relatively few reports of ceftriaxone-induced neutropenia. Our search identified a total of 16 individual cases; 3 [17, 18] were excluded from this analysis because the ANC never fell below 500/mm^3. Details of 14 cases (ours and 13 previously described ones) are summarized in Table 1. Under the Naranjo algorithm [3], a "probable" relationship was found between ceftriaxone and neutropenia in every case. The mean age of patients was 54 years (median, 57; range, 30–80 years) with 8 males and 6 females. Twelve patients received the usual recommended dosages of ceftriaxone (1–2 g daily); 2 patients (including ours) were treated with 4 g daily.

Consistent with earlier reports of nonchemotherapy drug-induced neutropenia [4, 19], the mean time to recognition of neutropenia was 23 days (standard deviation ± 14; median, 21 days; range, 5–49 days). The mean ANC nadir was 106/mm^3 (median = 51), with 3 cases, including ours, falling to 0 [9, 16].

Fever is often the first sign of drug-induced acute neutropenia [1], as seen in our patient, and was the most common manifestation in this case series (Table 1). One patient, who was pregnant [15], died from complications of her neutropenia. Neutrophil counts returned to normal levels (ANC >1500 mm^3) within a mean of 7 days (median, 5; range, 1–18) after discontinuation of ceftriaxone. The mean time for recovery from neutropenia was 2 days in the 2 surviving patients who received granulocyte colony-stimulating factor (G-CSF), compared with 8 days in 11 patients not treated with G-CSF.

The pathogenesis of ceftriaxone-induced agranulocytosis remains uncertain [1, 6, 7], and it is suggested to occur either by an immunologic mechanism or as a result of toxicity. However, careful analysis of the clinical findings and bone marrow histology in the 14 cases that we identified (Table 1) favor an immunologic mechanism over drug toxicity in many instances: (1) two patients [10, 13] had previously documented allergic reactions to penicillin; (2) one patient [15] received ceftriaxone 2 g for 15 days; the drug was discontinued and restarted 3 weeks later, and within 5 days neutropenia appeared; (3) 12 of the 14 patients received only moderate doses of ceftriaxone (1–2 g daily); (4) decreases in red blood cells and/or platelets occurred in only 2 of 14 cases [11, 13]; and (5) when bone marrow findings were included, they reported "myeloid maturation arrest" [5, 7, 9, 11, 12, 15]. These factors favor the hypothesis that antibody-dependent destruction of cells in the myeloid lineage caused the neutropenia [20]. The cell destruction in penicillin-induced neutropenia has been shown to result from the penicillin metabolite, which binds to protein conjugates, creating potentially immunogenic haptens [21]. Cephalosporin side chains are believed to constitute the major determinants of cephalosporin allergy; cross-reactivity between cephalosporins and penicillins often reflects similarities of side chain structures rather than the core [21]. Immunoglobulin G antibodies reacting with granulocytes have been identified in neutropenia due to other cephalosporins but not in cases attributed to ceftriaxone [22].

Prolonged treatment with high doses of ceftriaxone, as seen in 2 reports [6, 8] and our patient, might cause global toxic suppression of bone marrow; however, red blood cells and platelets would have been likely affected, and the bone marrow would show depression of all lineages [23]. A bone marrow examination was not done in these 3 cases, but apart from the agranulocytosis, their hematological parameters remained within normal limits or unchanged from baseline.

Ceftriaxone was discontinued once neutropenia appeared in all cases except 1, in which the patient [6] had just completed a 6-week course of therapy. In our case, ceftriaxone was not initially recognized as a possible cause of neutropenia; when this drug was discontinued, cefepime and vancomycin were added to broaden coverage for neutropenic fever. It is noteworthy that our patient recovered his neutrophils in spite of being treated with cefepime, because cefepime and ceftriaxone have similar structures with identical core and R1 side chain (Figure 1). The R2 side chain of ceftriaxone has triazinedione group, which

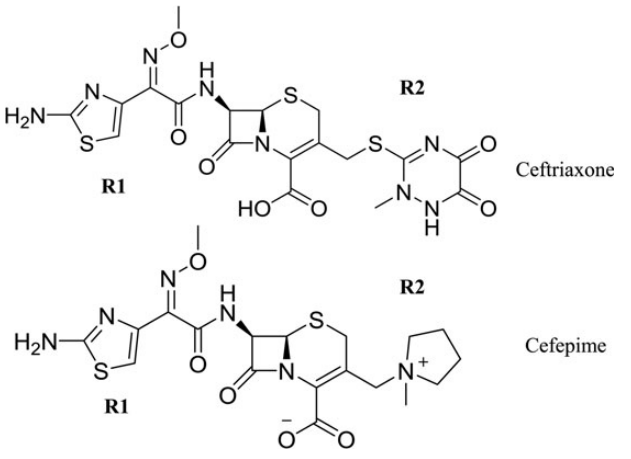

Figure 1. Structures of ceftriaxone and cefepime. In the R2 side chain position, ceftriaxone contains the more reactive triazinedione group, whereas cefepime contains a methylpyrollidinium moiety.

is more reactive than the methylpyrollidinium moiety in cefepime (Figure 1). If an immunologic mechanism was the cause, an antibody to the unique R2 side chain of ceftriaxone would likely have been responsible for the agranulocytosis because the patient responded to cefepime without complication.

CONCLUSION

Studies of ceftriaxone-associated neutropenia are limited to case reports and case series. We now present the most complete case review of ceftriaxone-induced agranulocytosis to date. Our findings suggest that an immunologic mechanism is responsible in most cases. In any patient whose ANC falls during an extended course of ceftriaxone therapy, ceftriaxone-induced agranulocytosis should be considered, and this drug should be discontinued. Although our patient recovered his granulocytes while being treated with cefepime, suggesting that an immunologic reaction was directed against the R2 side chain of ceftriaxone, we do not recommend such treatment in patients with ceftriaxone-induced neutropenia.

Acknowledgments

Author contributions. All authors have seen and approved the manuscript and contributed significantly to the work.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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