CASE REPORT

Meropenem-Induced Neutropenia in a Neonate

Joseph S. Van Tuyl, PharmD,¹ Aubrey N. Jones, PharmD,² and Peter N. Johnson, PharmD³

¹Department of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, Missouri; ²Moses Cone Hospital, Greensboro, North Carolina; ³Department of Pharmacy: Clinical and Administrative Sciences, University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma

Postmarketing surveillance has associated meropenem with the development of hematologic abnormalities, including agranulocytosis, neutropenia, and leukopenia, but the exact incidence in children is unknown. The case describes a full-term, 26-day-old neonate admitted for a sepsis workup. She was found to have a blood culture positive for *Enterobacter cloacae* and suspected meningitis and was initiated on meropenem 40 mg/kg/dose intravenously every 8 hours. On day 14 of antibiotic treatment, the patient developed an isolated neutropenia with an absolute neutrophil count of 288 cells/mm³. Meropenem was discontinued on hospital day 20, and a follow-up complete blood cell count 2 months later confirmed resolution of the hematologic abnormality. Clinicians should monitor complete blood cell counts diligently in children who receive large doses and prolonged courses of meropenem.

INDEX TERMS: adverse effect, carbapenem, child, meropenem, neonate, neutropenia, pediatric

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INTRODUCTION

Non-chemotherapy, drug-induced agranulocytosis is a rare adverse effect that is defined as an absolute neutrophil count (ANC) less than 1500 cells/mm³. It occurs during treatment or within 7 days of prior exposure to a drug and is associated with recovery of the ANC to >1500 cells/mm³ within 1 month of discontinuation of the offending agent.¹ Several medication classes have been implicated as etiologies, including beta-lactam antibiotics.^{2,3} Ibañez et al⁴ conducted a case-control epidemiological surveillance study of 78.7 million cases to assess the incidence of drug-induced agranulocytosis. They identified 396 confirmed cases of agranulocytosis with an overall incidence of 5.02:1 million inhabitants per year. Agranulocytosis substantially increased the risk of mortality, with an overall case-fatality rate of 9.1%. The drugs most commonly attributed in this study were dipyrone (16%), beta-lactam antibiotics (12.01%), ticlopidine (11.1%), antithyroid drugs (7.21%), and sulfonamide antibiotics (5.44%).⁴

Drug-induced neutropenia is a subclassification of agranulocytosis specific to neutrophils

that has been associated with beta-lactam antibiotics. Meropenem is a carbapenem with broad-spectrum coverage of Gram-positive and Gram-negative aerobic and anaerobic microorganisms. Common adverse effects observed in the pediatric population include diarrhea, rash, nausea, vomiting, and glossitis.⁵ However, postmarketing reports have linked meropenem to the development of hematologic abnormalities, such as agranulocytosis, neutropenia, and leukopenia, but the exact incidence cannot be calculated due to an unknown sample size.^{6,7} The following report describes the development of neutropenia in a neonate with bacteremia and suspected meningitis.

CASE REPORT

A 26-day-old female (4.8 kg) was transferred to the hospital with a recurrence of Gram-negative bacteremia. The patient was born at 39 weeks' gestation via a Caesarian section. A vacuum and forceps aided the delivery, and the patient experienced minor bruising of the head and chest. Neither the patient nor the mother received antibiotic therapy immediately prior to or after

Table 1. Complete Blood Cell Count in Relation to Meropenem Therapy

	Day 2	Day 14	Day 15	Day 17	Day 20	Follow-Up
WBC (10^3 cells/mm ³)	16.1	7.2	5.7	7.9	8.8	20.42
ANC (cells/mm ³)	9338	288	456	632	264	6698
Hgb (g/dL)	13.2	8.9	8.9	9.1	8.7	14.8
Hct (%)	38.8	25.3	25.5	26.3	25.7	41.6
Plt (10^3 cells/mm ³)	288	431	399	397	420	337

ANC, absolute neutrophil count; Hct, hematocrit; Hgb, hemoglobin; Plt, platelet; WBC, white blood cell

birth. The mother denied a history of urinary tract infections, sexually transmitted diseases, vaginal lesions, herpes infections, or rashes or lesions over the course of the pregnancy and tested negative for Group B streptococcus and human immunodeficiency virus. Fifteen days prior to the current hospitalization, the patient was admitted to an outside hospital and found to have an *Escherichia coli* bacteremia and pyelonephritis. The infection was treated with a 10-day course of intravenous (IV) cefotaxime and ampicillin. The patient was readmitted to the outside hospital 4 days after discharge when she developed a fever of 101°F. Blood cultures were collected, and an attempted lumbar puncture was unsuccessful. Despite empiric antibiotic therapy with IV cefotaxime and ampicillin, the patient remained febrile on the second day of hospitalization and was subsequently transferred to our hospital for further diagnostic evaluation and care.

Empiric antibiotic therapy with IV cefotaxime and ampicillin was continued after the transfer. On hospital day 1, repeat peripheral blood and cerebrospinal fluid (CSF) cultures were collected. Her baseline complete blood cell (CBC) count included a white cell count of 16.1 cells/mm³ with an ANC of 2898 cells/mm³ (Table 1). The initial lumbar puncture was traumatic, thereby preventing a definitive interpretation of the results (Table 2). Blood cultures from the outside hospital revealed *Enterobacter cloacae* resistant to third generation cephalosporins, but susceptible to meropenem. A description of antibiotics administered during this admission are noted in the Figure. Ampicillin and cefotaxime were discontinued on day 2, and a repeat lumbar puncture and CSF culture were obtained. Meropenem 40 mg/kg/dose IV every 8 hours was started secondary to culture and susceptibility data. Infectious disease was consulted and recommended the addition of tobramycin 3 mg/

kg/dose IV every 8 hours for synergistic activity for 72 hours until the CSF results from hospital days 1 and 2 were resulted. On day 3, her serum creatinine was 0.36 mg/dL, and her tobramycin serum trough concentration was elevated at 3.7 mg/L. The infectious disease team recommended changing tobramycin to gentamicin 2.5 mg/kg/dose IV every 12 hours. After 2 doses, gentamicin was discontinued due to the persistently elevated serum trough concentrations and risk of nephrotoxicity.

Additional diagnostic tests were performed in an attempt to identify the etiology of the patient's recurrent Gram-negative bacteremia. An immunoglobulin panel revealed that her immunoglobulins were on the lower end of the reference range, suggesting a possible immunodeficiency. However, her CD4 and CD8 were within normal limits, so severe combined immunodeficiency was eliminated as a diagnosis. On hospital day 5, she was found to have grade 3 vesicoureteral reflux on a voiding cystourethrogram.

Because meningitis could not be ruled out, due to a traumatic lumbar puncture on day 1, the infectious disease specialist recommended that meropenem be continued for 21 days. The patient remained afebrile and free of complications while receiving antibiotics. However, on day 13 of meropenem, the patient developed neutropenia with an ANC of 288 cells/mm³ and anemia. The anemia was attributed to a physiologic nadir (Table 1). A CBC count the following day demonstrated continued neutropenia with an ANC of 456 cells/mm³. The hemoglobin and hematocrit remained stable but were slightly low with an elevated reticulocyte count at 3.3%. Infectious disease suggested that therapy be continued and that ANC be monitored. Over the next few days, the ANC continued to improve with an ANC of 632 cells/mm³ on day 16 of meropenem. On day 19 of meropenem, the severity of the neutrope-

Table 2. Cerebrospinal Fluid Analysis

CSF Cell Count/Differential	Hospital Day 1	Hospital Day 2	Reference Values
Color	Red	Yellow	Colorless
Appearance	Clotted	Clear	Clear
WBC	NP	16	0-5/mm ³
RBC	NP	1065	0/mm ³
Neutrophils	NP	11	0%-6%
Lymphocytes	NP	38	40%-80%
Monocytes	NP	47	15%-45%
Eosinophils	NP	3	0%-2%
Macrophage	NP	1	0%-0%
Glucose	67	32	60-80 mg/dL
Protein	2694	130	20-120 mg/dL

CSF, cerebrospinal fluid; NP, not performed; RBC, red blood cell; WBC, white blood cell

nia worsened with an ANC of 264 cells/mm³. Meropenem was discontinued as the benefits of continuing therapy no longer exceeded the risk of complications from persistent neutropenia.

On day 21 the patient was discharged on antibiotic prophylaxis with nitrofurantoin 2 mg/kg/dose orally every 24 hours. Although a follow-up CBC count was scheduled for 1 week after discharge, the patient was lost to follow-up and additional labs were not obtained until about 2 months after discharge. A CBC count obtained at that time was unremarkable. There was no further evidence of neutropenia (ANC of 6698 cells/mm³), and the iatrogenic anemia had resolved.

DISCUSSION

To our knowledge, this is the first report of neutropenia associated with meropenem in a neonate. Only 1 case report has described neutropenia due to meropenem. Estella and colleagues⁸ reported the development of leukopenia, neutropenia, thrombocytopenia, and anemia in a 3-year-old patient. This patient initially received meropenem 40 mg/kg/dose every 8 hours after CSF cultures grew *Morganella morganii* susceptible to meropenem. Cultures remained negative for 2 weeks until *M morganii* was isolated again. The dose was subsequently increased to 100 mg/kg/dose every 8 hours, which is well above the dose that was used in our patient. Two weeks after dose escalation, the patient developed leukopenia, neutropenia, thrombocytopenia, and anemia. A bone marrow aspirate and biopsy

revealed hypoplastic and hypocellular marrow. Meropenem was discontinued. Two weeks later, a repeat CBC count showed resolution of the leukopenia and neutropenia despite the persistence of a mild anemia.⁸

Another report by Fariñas et al⁹ described the development of neutropenia in a 22-year-old female given 4 g/day of imipenem-cilastatin, also a carbapenem, for treatment of mandibular osteomyelitis. On day 19 of antibiotics, a marked decrease in the ANC to 900 cells/mm³ prompted a reduction in the dose of imipenem-cilastatin to 2 g/day. Two days after the dosage reduction, the ANC continued to decline (400 cells/mm³) and imipenem-cilastatin was discontinued. The hematologic abnormality resolved 6 days later (ANC 6300 cells/mm³). The patient was re-challenged with imipenem-cilastatin 2 g/day, but an abrupt decrease in the ANC (1400 cells/mm³) prompted permanent discontinuation of the antibiotic. The neutropenia resolved 7 days after antibiotic discontinuation.

The onset of neutropenia and subsequent recovery after discontinuation of meropenem in the current case is consistent with previous reports and observational studies. Olatson et al¹⁰ conducted a prospective study evaluating the incidence of hypersensitivity reactions and neutropenia in patients receiving beta-lactams for infective endocarditis. The occurrence of neutropenia appeared to be related to the duration of therapy, as no cases of beta-lactam-induced neutropenia occurred before 17 days of treatment. In our case, neutropenia developed after

Figure. Antibiotic regimen.

13 days of meropenem. The recovery of the ANC after discontinuation of the offending drug is often prolonged, as well, and instances of neutropenia have persisted for a mean of 10 days.¹¹ It is difficult to ascertain when the neutropenia resolved in our case. A repeat CBC count was not performed on the day of discharge; however, she was noted to have a normal CBC count approximately 2 months later.

Mechanisms of drug-induced neutropenia are primarily thought to be immune mediated or through direct toxicity to bone marrow. Proposed mechanisms include hapten formation, complement-mediated cell destruction, antibody-mediated cell destruction, and direct toxicity of myeloid precursors.^{2,3} In vitro analysis of beta-lactam antibiotics, including penicillin G, cloxacillin, and ceftizoxime, demonstrated dose-dependent inhibition of granulopoiesis, and analysis of bone marrow aspirates from cases of beta-lactam-induced neutropenia revealed few well-differentiated myeloid cells with abundant granulocyte precursors present.¹² Additionally, 2 cases of neutropenia due to large doses of cephalosporin exhibited antibody-mediated neutrophil destruction wherein the antibody reacts with the cephalosporin-coated neutrophil.¹³ The absence of a bone marrow aspirate and drug-dependent antibody testing preclude a definitive conclusion regarding the mechanism of meropenem-induced neutropenia for the current case. An elevated reticulocyte count for the current patient does not exclude the possibility of inhibition of granulopoiesis, as this is likely

a reflection of recovery from a mild anemia and previous reports exhibited preserved erythropoiesis. It is, therefore, plausible the mechanism of meropenem-induced neutropenia is similar to previous reports in which beta-lactams caused neutropenia through an inhibition of granulopoiesis or antibody-mediated destruction.

The patient received additional antibiotics during hospitalization that have been reported

to cause neutropenia. She initially received antimicrobial therapy with ampicillin, cefotaxime, tobramycin, and gentamicin prior to the initiation of meropenem on day 2. However, none of the other antibiotics had been administered to the patient in the 10 days prior to the development of the adverse effect. The patient had received large doses of meropenem (40 mg/kg/dose) for 13 days prior to the onset of neutropenia, which is consistent with previous reports of beta-lactam-induced neutropenia. Additional medications received during the hospitalization included acetaminophen, simethicone, and topical lidocaine; these were excluded as possible etiologies because they were administered as needed and administration did not correlate with the onset of the adverse event.

An alternative, known etiology of neutropenia is sepsis. Although the patient presented with a Gram-negative bacteremia at the outside hospital, peripheral blood cultures obtained on days 1 and 3 demonstrated no growth of microorganisms, indicating antibiotic therapy was effective and the sepsis was resolving. Application of the Naranjo Probability Scale¹⁴ in our patient indicated a "probable" (score 5 of 10) relationship between the adverse effect and administration of meropenem.

Hematologic abnormalities, including neutropenia, have been previously described for carbapenems and other beta-lactam antibiotics. The onset of the adverse effect correlates with the initiation of meropenem, and this conclusion is corroborated by additional published

evidence. A follow-up CBC count also confirmed resolution of neutropenia after discontinuation of meropenem.

CONCLUSIONS

In the current case, neutropenia occurred after approximately 14 days of meropenem. Clinical follow-up documented recovery of the ANC approximately 2 months after discharge. Despite a lack of prompt follow-up, the patient experienced no infectious complications from the neutropenia, which suggests recovery of the ANC occurred relatively quickly after discontinuation of antibiotic therapy. Given the serious health complications that may arise from neutropenia, clinicians should vigilantly monitor CBC counts in children receiving large doses or prolonged duration of meropenem.

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Abbreviations ANC, absolute neutrophil count; CBC, complete blood cell; CSF, cerebrospinal fluid; IV, intravenous

Correspondence Joseph S. Van Tuyl, PharmD, BCPS, St. Louis College of Pharmacy, 4588 Parkview Place, St. Louis, MO 63110, email: joseph.vantuyl@stlcop.edu

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