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Case Report

A newborn with anaphylaxis due to vancomycin

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ABSTRACT

Background. All drugs may cause hypersensitivity reactions. Anaphylaxis is a medical emergency that rarely occurs in newborns due to immature immunity. Early diagnosis and treatment are life-saving. Vancomycin, a glycopeptide antibiotic with bactericidal action against Gram-positive bacteria, is commonly used for neonatal nosocomial sepsis.

Case. We hereby present a premature infant (born at the 33rd week of gestation, birth weight: 1745 grams) who was started on vancomycin on postnatal day 7. He had severe circulatory failure and stridor during infusion on day 7 of vancomycin treatment and his tryptase level was elevated to 64.60 micrograms/L

Conclusions. To the best of our knowledge, there is no neonatal case of anaphylaxis due to vancomycin in the literature. Neonatologists should keep in mind that an anaphylactic reaction with a fatal course may develop during vancomycin infusion.

Key words: newborn, anaphylaxis, vancomycin.

Anaphylaxis is a life-threatening systemic hypersensitivity reaction that develops acutely. In epidemiological studies, its lifetime prevalence has been reported to be 0.05-2%.[1] However, the prevalence of anaphylaxis in infants remains unknown.[2] In a European anaphylaxis registry with 1970 patients younger than 18 years, 18 patients were under age one-year (0.9%)[3] The frequency of anaphylaxis under the age of 2 years has been gradually increasing over the years.[2] Common triggers in children are often foods, drugs, and insect venom.[4] While hypersensitivity reactions are common in children, anaphylaxis is very rare in newborns due to immature immunity.[5]

Vancomycin is a glycopeptide antibiotic with bactericidal action against Gram-positive bacteria. It is commonly used in nosocomial neonatal sepsis. To the best of our knowledge, anaphylaxis due to vancomycin has not been reported in newborns as yet. We hereby present a premature infant who had anaphylaxis due to vancomycin.

Case Report

A male baby born to a 24 year - old mother via cesarean section at the 33rd week of gestation, with a birth weight of 1745 grams, with a 1st minute Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score of 7 and 5th minute APGAR score of 8, was admitted to the neonatal intensive care unit (NICU) due to respiratory distress. He was moderately well and his vital signs were, body temperature: 36.6°C, respiratory rate: 60/min heart rate: 141/min. blood pressure: 44 / 22 (32) mmHg, oxygen saturation: 97%. He had bilateral retractions, tachypnea and grunting. He was placed on nasal intermittent positive pressure ventilation (IPPV) and started on 70 mL/kg of fluids and 5 micrograms/kg/min of dopamine. Intravenous ampicillin and gentamicin were started after blood cultures were drawn. Chest X-ray revealed air bronchograms and ground glass appearance,

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so 200 mg/kg of surfactant was administered on day 1. In the follow-up of the patient, there was no need for inotropes, enteral feeding was started. Abdominal distension developed on the 7th day of the patient and his abdominal X-ray and abdominal ultrasound were within normal limits. Enteral feeding was discontinued. An orogastric tube was inserted and placed in free drainage. The patient's white blood cell (WBC) count increased to 9,960/mm^3, platelet (PLT) count increased to 38,000/mm^3, and C-reactive protein (CRP) increased to 10 mg/L, hematocrit was 59%, hemoglobin level was 20 g/dL (Table I). The patient was switched to vancomycin and amikacin. He was weaned off nIPPV and oxygen on day 9. The patient developed stridor, desaturation and circulatory failure within ten minutes of vancomycin (10 mg/kg) infusion on day 14. His blood pressure at the time was 25/9 (14) mmHg, oxygen saturation (SpO2) was 84% and heart rate was 184 beats per minute. Free flow oxygen was provided and vancomycin was stopped immediately. Intravenous adrenaline and methylprednisolone and a 10 mL/kg saline bolus were administered. Serum tryptase level obtained 30 minutes after the episode was 64.6 (0-11.4) μg/L. Vital signs remained normal thereafter and no further vasopressors were needed. Echocardiogram was normal. On the 15th day, blood values were CRP level 2,2 mg/L, hematocrit 54%, hemoglobin level 18.8 g/dL, PLT count 191.000/mm3 and WBC count 12860/mm3 (Table I). Antibiotics were stopped, and the patient remained stable thereafter, tolerating gradually increasing enteral nutrition. His cultures remained negative, and he was discharged on day 30 in good condition. Consent was obtained from the patient's relatives for the publication of this case report.

Discussion

The case presented here is the first newborn who developed anaphylaxis due to vancomycin. In neonatal units, empirical treatment of late-onset sepsis is tailored to common pathogens and antibiotic susceptibility. Vancomycin, a glycopeptide with bactericidal activity against such Gram-positive agents as coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus* and enterococci, is a common empirical option.[6,7] Vancomycin was initiated empirically in our patient with a preliminary diagnosis of late onset sepsis, prompted by feeding intolerance, lethargy, thrombocytopenia and increasing CRP levels on postnatal day 7.

Common side effects of vancomycin are nephrotoxicity, ototoxicity, thrombocytopenia, agranulocytosis and phlebitis.[8] Another common side effect is vancomycin flushing syndrome (VFS), a hypersensitivity reaction, also known as "red man syndrome". It is an infusion reaction due to rapid infusion rather than a true allergic reaction. Unlike allergic reactions, it can occur with the first dose. It is characterized by flushing, erythema and itching, especially on the face and neck. Dyspnea and hypotension may also occur.[9,10] VFS is rarely life-threatening.[11] In animal studies, vancomycin was shown to directly activate mast cells, resulting in the release of vasoactive mediators such as histamine.[12] Renz et al.[13] found that when they administered 1000 mg of vancomycin over 10 minutes to 10 presurgical patients, all patients developed VFS, 7 had serious skin reactions and 5 had hypotension. VFS associated with vancomycin use has long been recognized as an adverse drug reaction.

Table I. Laboratory results of the patient.

	1st day	7th day	15th day
Hemoglobin (g/dL)	17.1	20	18.8
Hematocrit (%)	50.3	59	54
Leukocytes (/mm^3)	29560	9960	12860
Thrombocyte (/mm^3)	82.000	38.000	191.000
C-reactive protein (mg/L)	6	10	2.2

However, few systematic investigations have been conducted on pediatric subjects to date. One previous retrospective study evaluated VFS in 650 children who had been exposed to vancomycin, and found a low rate (1.6%) of VFS, which limited their ability to determine risk factors.[14] Deo et al.[15] have recently published a review where they report a total of 11 cases of VFS in the last 8 years, four of which were children. Only a small number of case reports of VFS have been published. One is a report of an infant born at the 32nd week of gestation and had VFS due to vancomycin started for femoral osteomyelitis, one was a newborn who had stridor and VFS after perioperative administration of vancomycin and one was a newborn who had severe hypotension and respiratory distress in addition to VFS while on high-dose vancomycin.[16] In our case, the dosing interval of vancomycin infusion was adjusted according to the gestational age, and it was administered at a dose of 10 mg/kg, diluted to 5 mg/ml concentration, and given as a one hour intravenous infusion. Flushing on the face and neck, which is typical in VFS, was not detected in our case. The main finding in our patient was severe hypotension, tachycardia and respiratory distress. Therefore, VFS was not considered.

Anaphylaxis is a sudden and potentially fatal condition that occurs as a result of exposure to an allergen without any prior symptoms. Therefore, prompt diagnosis and treatment are very important. The prevalence of anaphylaxis in infants remains unknown. One study reported an annual incidence of 0.5/100,000.[17] Anaphylaxis is very rare in newborns due to their immature immunity.[5] There are few case reports about neonatal anaphylaxis in the literature. Kendigelen et al.[18] detected tachypnea, tachycardia, and mild angioedema that developed suddenly during amikacin infusion on the 3rd postnatal day in a premature infant born at 33 weeks of gestational age, and they found that the infant improved rapidly upon the cessation of the amikacin infusion and adrenaline administration. The clinical findings recurred after one hour. The authors suggested that sodium metabisulphite that is present in the amikacin solution was what caused the anaphylaxis. Koklu et al.[19] reported three newborns who had anaphylaxis due to intramuscular vitamin K, intravenous levatiracetam and fluconazole, respectively.

Neonatal anaphylaxis due to vancomycin has not been reported as yet. Patients with anaphylactic reactions due to vancomycin usually have a history of multiple previous exposures. Anaphylaxis is predominantly a clinical diagnosis and involves the skin (itching, urticaria, facial erythema, angioedema), gastrointestinal tract (abdominal pain, vomiting, diarrhea), upper and lower respiratory system (rhinitis, hoarseness, laryngeal edema, stridor, dyspnea, cough, wheezing) and the cardiovascular system (dizziness, hypotension, syncope, shock).[20] Although skin symptoms are predominant in adults in anaphylaxis, the primary presentation in children may be respiratory in some cases.[21] In our case, sudden onset of severe hypotension, tachycardia, stridor and low saturation were detected on day 7 of vancomycin infusion. The findings in neonatal anaphylaxis reported in the literature are cyanosis, tachycardia, hypotension, multiple organ failure with coagulopathy, edema of the eyelids and epiglottis, reduced peripheral perfusion, poor sensorium, flaccidity, apnea, bradypnea and bradycardia, erythematous rashes, urticaria, hypotension and shock. Obviously, neonatal symptoms can easily be confused with sepsis. However, in anaphylaxis, rapid diagnosis and correct treatment are life-saving. In the cases reported in the literature, except for the case who developed anaphylaxis due to cow's milk-based formula, all of these findings were considered to be anaphylaxis, and rapid recovery was observed with adrenaline, steroids, respiratory and circulatory support.

The fact that our patient deteriorated extremely precipitously prompted us to consider anaphylaxis. Due to the poor general condition of the patient and the open vascular access, adrenaline was administered intravenously. Fortunately, the patient improved rapidly upon

the cessation of vancomycin and administration of adrenaline and corticosteroids.

The main effector cells of systemic anaphylaxis are mast cells and basophils. During an anaphylaxis episode, mast cells release mediators such as tryptase, histamine and platelet activating factor. Measurement of histamine levels and tryptase levels can be used in the diagnosis of anaphylaxis. Blood samples should be drawn after 30-120 min of symptom onset.[22] In a recent study examining tryptase levels in children presenting with anaphylaxis, tryptase levels were found to be high in only 19.2% of children, and only severe reactions were associated with levels of 11.4 micrograms/L or higher.[23] Our patient's tryptase level was 64.6 micrograms/L in the serum sample obtained 30 minutes after the onset of anaphylaxis. Severe elevation in serum tryptase level supports that our patient had anaphylaxis due to vancomycin.

In conclusion, anaphylaxis is a clinical emergency. Early diagnosis and treatment are lifesaving. It should be kept in mind that anaphylaxis may occur during vancomycin infusion which is frequently used in neonatal intensive care units.

Ethical approval

Informed consent was obtained from the family for the publication of this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: EB, BA; data collection: EB, BA; analysis and interpretation of results: EB,BA; draft manuscript preparation: EB,BA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol 2006; 97: 596-602. https://doi.org/10.1016/S1081-1206(10)61086-1
2. Simons FER, Sampson HA. Anaphylaxis: Unique aspects of clinical diagnosis and management in infants (birth to age 2 years). J Allergy Clin Immunol 2015; 135: 1125-1131. https://doi.org/10.1016/j.jaci.2014.09.014
3. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. J Allergy Clin Immunol 2016; 137: 1128-1137.e1. https://doi.org/10.1016/j.jaci.2015.11.015
4. Anagnostou K. Anaphylaxis in children: epidemiology, risk factors and management. Curr Pediatr Rev 2018; 14: 180-186. https://doi.org/10.2174/1573396314666180507115115
5. Simons FER. Anaphylaxis: recent advances in assessment and treatment. J Allergy Clin Immunol 2009; 124: 625-636; quiz 637-638. https://doi.org/10.1016/j.jaci.2009.08.025
6. Edwards MS, Baker CJ. Sepsis in the newborn. In: Gershon AA, Hotez PJ, Katz SL (eds). Krugman's Infectious Diseases of Children. St Louis: Mosby, 2004: 545-561.
7. Lutsar I, Chazallon C, Carducci FIC, et al. Current management of late onset neonatal bacterial sepsis in five European countries. Eur J Pediatr 2014; 173: 997-1004. https://doi.org/10.1007/s00431-014-2279-5
8. Machado JKK, Feferbaum R, Kobayashi CE, Sanches C, Santos SRCJ. Vancomycin pharmacokinetics in preterm infants. Clinics (Sao Paulo) 2007; 62: 405-410. https://doi.org/10.1590/s1807-59322007000400006
9. Symons NL, Hobbes AF, Leaver HK. Anaphylactoid reactions to vancomycin during anaesthesia: two clinical reports. Can Anaesth Soc J 1985; 32: 178-181. https://doi.org/10.1007/BF03010047
10. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. Anesth Analg 2003; 97: 1381-1395. https://doi.org/10.1213/01.ANE.0000082993.84883.7D

11. Glicklich D, Figura I. Vancomycin and cardiac arrest. Ann Intern Med 1984; 101: 880. https://doi.org/10.7326/0003-4819-101-6-880_2

12. Veien M, Szlam F, Holden JT, Yamaguchi K, Denson DD, Levy JH. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. Anesthesiology 2000; 92: 1074-1081. https://doi.org/10.1097/00000542-200004000-00026

13. Renz CL, Thurn JD, Finn HA, Lynch JP, Moss J. Oral antihistamines reduce the side effects from rapid vancomycin infusion. Anesth Analg 1998; 87: 681-685. https://doi.org/10.1097/00000539-199809000-00036

14. Myers AL, Gaedigk A, Dai H, James LP, Jones BL, Neville KA. Defining risk factors for red man syndrome in children and adults. Pediatr Infect Dis J 2012; 31: 464-468. https://doi.org/10.1097/INF.0b013e31824e10d7

15. Deo S, Rai SK, Moudgil K. Red man syndrome in vancomycin care patients-a critical review. Journal of Critical Reviews 2020; 7: 315-317. https://doi.org/10.31838/jcr.07.05.59

16. Martini S, Alessandroni R, Arcuri S, Faldella G. Vancomycin-induced red man syndrome presentation in a preterm infant. Pediatr Dermatol 2018; 35: e408-e409. https://doi.org/10.1111/pde.13654

17. West SL, D'Aloisio AA, Ringel-Kulka T, Waller AE, Clayton Bordley W. Population-based drug-related anaphylaxis in children and adolescents captured by South Carolina Emergency Room Hospital Discharge Database (SCERHDD) (2000-2002). Pharmacoepidemiol Drug Saf 2007; 16: 1255-1267. https://doi.org/10.1002/pds.1502

18. Kendigelen P, Baktir M, Sucu A, Kaya G. Anaphylaxis after administration of amikacin containing sodium metabisulfite in a premature newborn. Arch Argent Pediatr 2016; 114: e195-e198. https://doi.org/10.5546/aap.2016.eng.e195

19. Koklu E, Taskale T, Koklu S, Ariguloglu EA. Anaphylactic shock due to vitamin K in a newborn and review of literature. J Matern Fetal Neonatal Med 2014; 27: 1180-1181. https://doi.org/10.3109/14767058.2013.847425

20. Wang J, Sampson HA. Food anaphylaxis. Clin Exp Allergy 2007; 37: 651-660. https://doi.org/10.1111/j.1365-2222.2007.02682.x

21. de Silva IL, Mehr SS, Tey D, Tang MLK. Paediatric anaphylaxis: a 5 year retrospective review. Allergy 2008; 63: 1071-1076. https://doi.org/10.1111/j.1398-9995.2008.01719.x

22. Simons FER, Ardusso LRF, Bilò MB, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol 2012; 12: 389-399. https://doi.org/10.1097/ACI.0b013e328355b7e4

23. De Schryver S, Halbrich M, Clarke A, et al. Tryptase levels in children presenting with anaphylaxis: Temporal trends and associated factors. J Allergy Clin Immunol 2016; 137: 1138-1142. https://doi.org/10.1016/j.jaci.2015.09.001