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Case Study

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CEFTAZIDIME-AVIBACTAM INDUCED BICYTOPENIA: A CASE REPORT

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ABSTRACT

Ceftazidime-avibactam is one of the most commonly used third generation cephalosporin antimicrobial agent, which has action against gram negative susceptible and other non susceptible pathogens. Several adverse effects have been reported with ceftazidime- avibactam. In this case report, we discuss one of the growing haematological adverse effects of Ceftazidime avibactam- bicytopenia in which the platelet count had risen within 24 hours after withdrawing the drug. Cases on ceftazidime-avibactam induced bicytopenia are under reported. The use of such drug for gram negative susceptible pathogens are increasing worldwide, hence these life-threatening adverse effects should be borne in mind during every treatment.

KEYWORDS: Ceftazidime -Avibactam, Bicytopenia, Gram Negative Organism, Pseudomonas aeruginosa.

INTRODUCTION

Ceftazidime is a third generation cephalosporin beta-lactam antibiotic having a broad spectrum activity and is used to prevent various bacterial infections such as lower respiratory tract infections, skin infections, urinary tract infections, CNS infections caused by susceptible bacteria. It is mostly used in combination with avibactam which is a non-beta lactamase beta lactamase inhibitor. This combination is also indicated in treating hospital acquired and ventilator associated bacterial pneumonia (HABP/VABP). Ceftazidime-avibactam has excellent in vitro activity against a variety of significant Gram-negative pathogens, including many isolates of Enterobacteriaceae. Similar to other beta-lactam antibiotics, ceftazidime largely exerts its bactericidal effect by directly inhibiting particular penicillin-binding proteins in sensitive bacteria. Ceftazidime primarily binds to PBP3, with weaker affinities for PBP1a/1b and PBP2 as well[[1]]. Both ceftazidime and avibactam exhibit low levels of human protein binding. They enter the bronchial epithelial lining fluid dose-proportionally, reaching concentrations of around 30% or greater at lower plasma doses.[2] They are not metabolised to any extend and are eliminated unchanged in the urine. Since they are significantly excreted by the kidney, the risk of adverse responses to ceftazidime and avibactam may be increased in individuals with impaired renal function. Phlebitis at the injection site; candidiasis; increased aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and prothrombin time; hypokalemia; hypersensitivity reactions are other adverse effects.[3]

Bicytopenia refers to a decrease in two blood lineages using the following criteria.

Haemoglobin (Hb):Men <13 g/dL;non pregnant women <12 g/dL

Platelets:<150, 000/microL

Drug induced bicytopenia is caused mostly by bone marrow suppression and humoral system activation. Here we report a case of ceftazidime -avibactam induced bicytopenia.

CASE REPORT

A 75 year old male patient came to the emergency department on 5/2/23 with complaints of fever, chills and intermittent episodes of cough with minimal expectoration. Patient had a known medical history of Traumatic brain injury, Type 2 Diabetes Mellitus and Hypertension. He had tracheostomy in-situ as lung toileting was done through trachestoma. Hence he was admitted to HDU in view of decreased response (GCS:E2VTM2), raised CRP levels(170mg/dL)and hypernatremia(158 mEq/L). Hence Ceftriaxone 1 gram IV Q12H was initiated along with other antidiabetic agents, antihypertensive medications with frequent position change, and salt free diet. Regular Blood counts and CRP monitoring was advised. His blood culture and sensitivity reports came out negative during these times and hence ceftriaxone was stopped (14/2/23). Sputum culture reports had showed normal upper respiratory flora. On 17/2/23 he was shifted to ICU in view of increasing sodium levels(178-166-164), where his chest X-ray had showed right sided pneumothorax. Hence in view of pneumothorax , HRCT and tracheostomy ET

MINIBAL culture and sensitivity was sent . His ET MINIBAL culture and sensitivity reports came out positive for Pseudomonas aeruginosa which was sensitive to ceftazidime (MIC 2, Breakpoint </=8). Hence ceftazidime-avibactam 1 gram IV TID was started on 22/2/23 soon after which his X-ray chest reports showed improvement. His laboratory parameters, especially platelet counts and haemoglobin levels which were normal before initiating ceftazidime-avibactam had started showing a decreased trend(Table 1). Patient's Hb at the time of admission was 10. 3 which had been dropping steadily, showed a sharp decline to a level of 6. 6 after 1 week of initiation of ceftazidime-avibactam. In view of Hb 6. 6, 1 pint PRBC infusion was given on 4/3/23. There was no anticoagulants or condition specific causes for thrombocytopenia for the patient and the decreasing trend was noticed only after ceftazidime-avibactam was initiated. Hence ceftazidime-avibactam was suspected to be the cause of bicytopenia. Therefore decision was made to stop the drug (5/3/23) following which his platelet counts were raised and reached normal range within 1 day. Patient was continued on folate and Vitamin B12 supplements for subsequent Hb elevation.

Table 1.

PARAMETERS	28/2/23	1/3/23	2/3/23	3/3/23	4/3/23	5/3/23 (Drug stopped)	6/3/23	7/3/23
HAEMOGLOBIN(mg/dl)	7. 5	7. 5	7. 4	6. 9	6. 6	8. 7	10. 3	11
PLATELETS (lakh/μL)	1. 61	1. 02	1. 00	0. 62	0. 60	0. 66	1. 09	1. 55

DISCUSSION

Thrombocytopenia is a condition characterised by a decreased number of platelets in peripheral blood, which can be caused by a myriad of both congenital and acquired disorders. DITP deserves a special focus since its cumulative incidence can be as high as 10 cases per million population per year, with a prevalence of approximately 25% in critically ill patients. This condition is usually suspected following identification of an acute and severe decrease in platelet count, with values usually < 50 ×109/L, thus potentially exposing patients to an increased risk of developing spontaneous haemorrhages.[4] Platelets are impacted substantially more frequently than other cell types for unidentified reasons. Reduced production, increased degradation, and dilution of platelets can all contribute to thrombocytopenia. Drug molecules create antibodies after covalently attaching to the platelet membrane protein, which causes platelet loss. Another viewpoint contends that acquiring these antibodies via blood transfusion from a donor can also cause platelet damage. Bone marrow suppression and immunological thrombocytopenia should be of concern during the examination of thrombocytopenia. If there has been a prior history of thrombocytopenia brought on by the same medicine, DITP typically manifests 1–2 weeks or even just a few days after the start of treatment.

Ceftazidime is a third-generation broad-spectrum cephalosporin that, like other -lactam antimicrobials, works by binding to PBPs and inhibiting peptidoglycan crosslinking during cell wall synthesis, resulting in bacterial cell lysis and death. In combination with avibactam it enhances ceftazidime-avibactam action by shielding ceftazidime from degradation by a range of serine-lactamases. In this case , patient's platelet counts was dropping at a steady level after 1 week of therapy with ceftazidime-avibactam. Moreover patients Hb drop was also suspected after ceftazidime-avibactam was started. Similar cases of platelet drop for a period of 12 days after 4 week therapy with ceftazidime-avibactam during a post-operative period has also been reported.[5]

Bicytopenia is a life-threatening adverse effect of ceftazidime-avibactam. There are about 5 case reports on ceftazidime-avibactam induced bicytopenia in Vigiaccess till date. The typical underlying mechanism of cephalosporin induced blood dyscrasias is a drug macromolecule linked hapten antibodies which activates humoral immune system. When a certain medication is suspected of causing bicytopenia, it should be stopped right away. This decision will be influenced by the severity of bicytopenia, the trajectory of blood counts, clinical symptoms, and the need for treatment.

CONCLUSION

This case presents a growing haematological adverse event of bicytopenia induced by ceftazidime-avibactam where the platelet count rose within 24 hours after withdrawing the drug and Hb within normal range after blood transfusion. Thus, if a patient on ceftazidime-avibactam therapy develops bicytopenia, the drug can be suspected as the possible offending agent after ruling out other possible causes. Blood transfusion can be performed as part of supportive therapy along with other supplementations.

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ABBREVATIONS

CNS: Central Nervous System
HABP:Hospital Acquired Bacterial Pneumonia
VABP:Ventilator Acquired Bacterial Pneumonia
PBP: Penicillin Binding Protein
HDU: High Dependency Unit
CRP: C-Reactive Protein

Q12H: Every 12 hours
HRCT: High-Resolution Computed Tomography
ET MINIBAL: Endotracheal mini-bronchoalveolar lavage
MIC: Minimum Inhibitory Concentration
TID: Thrice Daily
PRBC: Packet Red Blood Cell
DITP: Drug Induced Thrombocytopenia
Hb: Haemoglobin

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