EJMI

DOI: 10.14744/ejmi.2019.84589
EJMI 2020;4(1):7–11

Research Article

Myelosuppression in Patients with Prolonged use of Piperacillin/Tazobactam

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Abstract

Objectives: The use of piperacillin-tazobactam in hospital acquired infections requiring long treatment periods may cause adverse effects including myelosuppression. Myelosuppression results in rare, but potentially serious clinic manifestations such as neutropenia, thrombocytopenia, leukemia and anemia. The objective of this study was to investigate the incidence and characteristics of myelosuppression in patients with prolonged use of piperacillin-tazobactam.

Methods: Inpatients followed-up and treated in Kahramanmaras Sutcu Imam University Medical Faculty Hospital and MMT Gaziantep American Hospital between April 1, 2017 and December 31, 2018 were included in the study. Patients' demographic data, biochemical laboratory outcome, duration and dose of antibiotic treatment, comorbidities, side effects of antibiotic therapy were recorded and analyzed.

Results: A total of 34 inpatients who received antibiotic therapy with piperacillin-tazobactam due to various diagnoses were included in the study. The mean duration of PTZ use was found as 11.9±6.31 days. Of all patients, 19 (55.9%) used antibiotics for longer than 10 days, while 15 (44.1%) used PTZ for 10 days or shorter. The mean duration of antibiotic use was found as 12.2 days in patients aged 65 years and over, while this duration was 11.5 days in patients aged under 65 years. Five patients (14.7%) developed neutropenia. Neutropenia was developed in 14.8 days of PTZ treatment on average. The mean duration of returning to normal values was found as 1.8 days in these patients. Neutropenia was developed at the 4th week of the treatment in 60% of these patients.

Conclusion: It should be kept in mind that myelosuppression may be encountered especially during prolonged PTZ therapy, and full blood count monitoring should be performed carefully and closely in these patients.

Keywords: Adverse effect, myelosuppression, nosocomial Infection, Piperacillin/Tazobactam

Cite This Article: *Şahin AR, Taşdoğan AM. Myelosuppression in Patients with Prolonged use of Piperacillin/Tazobactam. EJMI 2020;4(1):7–11.*

Piperacillin-tazobactam (PTZ), a combination of piperacillin, which is a semisynthetic ureidopenicillin, is a broad antibacterial spectrum beta lactam class antibiotic.[1] Piperacillin-tazobactam is used in critically ill patients for the treatment of pneumonia, intra-abdominal infections (peritonitis, appendicitis, cholangitis, cholecystitis), urinary tract infections and infections caused by sensitive bacteria. PTZ treatment can be empirically initiated in febrile neutropenia, hospital acquired sepsis, and hospital infections caused by Pseudomonas aeruginosa. PTZ has found a wide area of usage and is commonly used in intensive care unit and/or hospital acquired infections.

The use of PTZ in hospital acquired infections requiring long treatment periods may cause adverse effects. Pro-

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Submitted Date: October 28, 2019 **Accepted Date:** December 05, 2019 **Available Online Date:** January 16, 2020

longed use of PTZ may lead to gastrointestinal complaints, pain in injection site in intramuscular injections, thrombophlebitis in repeating intravascular infections, transient increases in aminotransferase levels, electrolyte derangements that may clinically cause more concerns, cardiac arrhythmias, neurologic problems, hypersensitivity reactions and myelosuppression.[2]

Myelosuppression is a critical problem in intensive care patients. Studies have shown a reversible relationship between PTZ and hematologic alterations caused by myelosuppression.[3] Neutropenia is a threat with high rate of mortality for patients receiving critical care. These patients are more vulnerable to infections, and the diagnosis is more challenging once infection occurs. Thrombocytopenia make the clinical judgement difficult since it may develop due to many reasons. Various case reports and cohort studies[4–6] a systematic review[7] have shown the presence of neutropenia, leukopenia, and pancytopenia related to PTZ treatment. However, the results of these studies suggest that these effects of PTZ depend on doses and duration of treatment.[8] It was thought that discussing the side effects of PTZ that are not uncommon in nosocomial infections would provide contribution to the existing literature.

The objective of this study was to investigate the incidence and characteristics of myelosuppression including neutropenia and thrombocytopenia in hospitalized patients with prolonged use of piperacillin-tazobactam.

Methods

Study Design and Area

This study was designed as retrospective and conducted in two centers. Kahramanmaras Sutcu Imam University Medical Faculty Hospital has a capacity of 529 beds with 120 being intensive care units. MMT Gaziantep American Hospital has a capacity of 86 beds with 13 being intensive care units. Inpatients who received PTZ treatment between April 1, 2017 and December 31, 2018 were screened from the hospital records. Patients were examined as those administered PTZ for longer than 10 days and the patients who received PTZ for shorter than 10 days. Patients with hematologic diseases, neutropenia detected before initiating PTZ treatment, patients without weekly blood count during treatment and those who received blood transfusion during hospitalization were excluded from the study.

Variables

In full blood count; low leukocyte count (<4000/μL) was considered as leukopenia, hemoglobin concentration <12 g/dL in women and <13 g/dL in men as anemia, and platelet count <150000 as thrombocytopenia. Neutrophils count <1500 cells/mm^3 was defined as neutropenia. Neutrophils count <500 cells/mm^3 was considered severe neutropenia. The defined hematologic changes were considered to be related to PTZ if these changes were developed during PTZ treatment, resolved after discontinuation of PTZ, and no other reason was found to explain neutropenia.

Ethics Approval

The study protocol was approved by Kahramanmaras Sutcu Imam University Medical Faculty Ethics Committee with 18/04/2018 dated and 104 numbered decision.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation. Descriptive variables were expressed as number and percentage. Pearson's Chi-square test and logistic analysis were used in statistical analysis of paired variables. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 20.0 (SPSS Inc, Chicago, IL, USA) package software.

Results

A total of 34 inpatients who received antibiotic treatment with PTZ due to various diagnoses were included in the study. The mean age of the patients was found as 61.0±26.5 years. Of all patients 22 (64.7%) were male and 12 (35.3%) were women. The mean age was found as 56.3±26.5 years in male and 69.5±23.5 years in female patients. Twenty-one patients (61.8%) aged 65 years and over and 13 patients (38.2%) under 65 years.

When admission diagnoses of the patients were examined; 16 (47.1%) was diagnosed with pneumonia, 10 (29.4%) sepsis, 3 (8.89%) pneumonia + sepsis, 1 (2.9%) wound site infection, 1 (2.9%) COPD, 1 (2.9%) Fournier's gangrene, 1 (2.9%) urinary tract infection and 1 (2.9%) soft tissue infection. In addition, comorbidities of the patients included CVE, epilepsy, diabetes mellitus, chronic renal failure, cirrhosis, asthma, angina pectoris and hypertension.

The mean duration of PTZ use was found as 11.9±6.31 days. Of all patients, 19 (55.9%) used antibiotics for longer than 10 days, while 15 (44.1%) used PTZ for 10 days or shorter. The mean duration of antibiotic use was found as 12.2 days in patients aged 65 years and over, while this duration was 11.5 days in patients aged under 65 years.

When biochemical analysis outcomes of the patients were evaluated; the mean WBC count was found as 8867 cells/mm^3, the mean HGB as 10.8 g/dL, the mean platelet count as 274.6x10^3 cell/mm^3, and the mean neutrophils count as 6724 cells/mm^3. The mean cumulative PTZ dose was calculated as 170.4±102.6 g. Of all patients, 64.7 (n=22) used

more than one antibiotic. The distribution of PTZ use and duration according to demographic features of the patients is given in Table 1.

Five patients (14.7%) developed neutropenia. Neutropenia was developed in 14.8 days of PTZ treatment on average. The mean duration of returning to normal values was found as 1.8 days in these patients. All patients who developed neutropenia were male. Neutropenia was developed at the 4th week of the treatment in 60% of these patients. Of the patients who developed neutropenia, 40% aged 65 years and over. Characteristics of the patients who developed neutropenia are shown in Table 2. Of all patients, 5 (14.7%) developed leukopenia, 14 (41.2%) thrombocytopenia and 25 (75.3%) anemia.

Discussion

Extended spectrum beta lactamase (ESBL) producing strains draw attention with increased mortality as the most common cause of hospital acquired bacteremia.[9] Carbapenems are commonly used in the treatment of infections caused by ESBL. However, the use of carbapenems has increased by three folds between 2010 and 2014.[10] Recent studies have reported that even a short exposure to carbapenems increases the colonization risk of carbapenem resistant bacteria in intensive care patients.[11] Therefore, new alternatives are being constantly searched for the treatment of these infections. Among these PTZ, which is a broad antibacterial spectrum beta lactam class antibiotic is used as an alternative to carbapenems in the treatment of infections caused by ESBL producing strains.

Myelosuppression may develop due to infections, metabolic disorders, chemicals, radiation, drugs and many other reasons. Antibiotics are known to cause myelosuppression as a side effect. Myelosuppression including neutropenia, thrombocytopenia and rarely hemolytic anemia is known as an adverse drug reaction of beta-lactam antibiotics. A recent systematic review supported the assumption that piperacillin may also have such adverse effects.[7, 12] Although this adverse effect of beta-lactam group drugs is not a frequently seen situation, case reports in our country on this issue have increased in recent years. Studies showing how this effect of beta-lactam antibiotics emerges are limited. In a study by Weiss et al.,[13] myelosuppression resulting in thrombocytopenia, anemia, and/or neutropenia develops when IgG or IgM antibodies binds to antimicrobial agents on the surface of circulating cells, leading to lysis or opsonization of these cells.

In the present study, we investigated the incidence and characteristics of myelosuppression and its results such as neutropenia, thrombocytopenia, leukopenia and anemia in patients with prolonged use of PTZ.

Neutropenia is a rare, but potentially serious complication of antibiotic treatment. Neutropenia is thought to be resulted from hypersensitivity reaction or suppression of white blood cells due to toxic doses.[14] Although mechanisms of neutropenia secondary to PTZ is not fully understood, neutropenia has been reported to be either an immune mediated reaction or an idiosyncratic reaction occurring directly due to myeloid damage.[2, 15–17] Thee development of neutropenia may be related to the duration of treatment. Neutropenia is often seen from the 10th day of antibiotic therapy.[18] In our study, 5 (14.7%) of the 34 patients developed neutropenia. In these patients, neutropenia was developed in 14.8 days of PTZ treatment on average. Neutropenia emerged at the 4th week of the treatment in 60% of these patients. In a study by Peralta et al.[8] investigating myelosuppression in patients diagnosed with bone

Table 1. Distribution of PTZ use and duration according to demographic features of the patients

	n	%	AB dose (g) Mean±SD	AB duration (days) Mean±SD
Overall	34	100	170.4±102.6	11.9±6.3
Gender				
Female	12	35.3	174.5±100.0	12.4±6.1
Male	22	64.7	168.1±102.6	11.6±6.3
Age				
<65 yo	13	38.2	148.4±104.0	11.5±6.4
≥65 yo	21	61.8	184.0±98.4	12.2±6.1
AB duration				
<10 days	15	44.1	78.8±81.4	5.3±4.4
≥10 days	19	55.9	227.1±98.4	16.0±6.0

Table 2. Characteristics of the patients who developed neutropenia

	Gender	Age (years)	Total PT dose (g)	AB duration (days)	Hemoglobin (g/dL)	WBC (cells/mm³)	PLT (x10³ cell/mm³)	Neutrophils (cell/mm³)
1	M	81	475	25	11.9	10950	323	640
2	M	66	310.5	23	9.1	6490	225	480
3	M	31	198	22	8.1	5350	213	360
4	M	33	306	17	9.6	19400	199	510
5	M	4	13	3	9.2	900	800	600

infection, 6 (20%) of the 30 patients who received PTZ for longer than 10 days developed neutropenia. In our study, 55.9% of the patients received antibiotics for longer than 10 days. In a study by Uzun et al.[19] with patients who received PTZ therapy due to diabetic foot infection, the incidence of neutropenia was reported as 6/31.

The mechanism of neutropenia is associated with cumulative piperacillin doses, and daily PTZ dose should not be considered the same for all patients. In our study, them mean cumulative PTZ dose was found as 170.4 grams. PTZ induced neutropenia is resolved by discontinuation of antibiotics. In a study by Lee et al.,[2] it was reported that WBC values were started to rise two days after stopping of antibiotic therapy in a patient who developed myelosuppression. Again Reichardt et al.[5] reported that side effects seen in children receiving PTZ due to fibrosis disappeared within the first 24 hours after discontinuing the drugs. In our study, the mean duration of returning to normal values was found as 1.8 days in patients who developed neutropenia, consistently with the literature.

Myelosuppression effect of PTZ is not limited with neutrophils and platelets may also be influenced. Common adverse reactions associated with PTZ include leukopenia and thrombocytopenia in addition to neutropenia;[20] these reactions typically occur simultaneously and thrombocytopenia is rarely seen independently from the other symptoms.[21] The mechanism by which PTZ causes thrombocytopenia is unclear. However, three underlying mechanisms have been proposed for drug induced thrombocytopenia: immune mediated, direct decrease in platelet count and myelosuppression.[22] It has not been well-determined that how many episodes of thrombocytopenia are related to drug use, but some observational studies have reported an incidence as high as 10%.[23] Platelet count begins to rise 2 days after discontinuing PTZ in patients developing thrombocytopenia.

In our study, 14 patients (41.2%) developed thrombocytopenia, and platelet counts were reached normal values in these patients after stopping PTZ. In a study by saltoglu et al. comparing the effectiveness of PTZ and imipenem/cilastatin in patients with soft tissue infection, 2 of 30 patients developed leukopenia and thrombocytopenia.[24]

In our study, the incidence and characteristics of myelosuppression was investigated in patients who received PTZ therapy. PTZ is a relatively novel drug used as an alternative to carbapenems. Studies on this issue are mostly case reports in the literature. Further comprehensive studies with a larger series of patients are needed in order to better determine mechanisms of these rare, but potentially serious complications of PTZ therapy.

Conclusion

It should be kept in mind that myelosuppression may be encountered especially during prolonged PTZ therapy, and full blood count monitoring should be performed carefully and closely in these patients. Relevant blood parameters were observed to rapidly improve in these patients after discontinuation of treatment. More studies are needed to determine the risk factors of developing neutropenia, thrombocytopenia, leukopenia, anemia and other clinical manifestations due to myelosuppression in patients receiving PTZ treatment.

Disclosures

Ethics Committee Approval: The study protocol was approved by Kahramanmaras Sutcu Imam University Medical Faculty Ethics Committee with 18/04/2018 dated and 104 numbered decision.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.R.Ş.; Design – A.R.Ş.; Supervision – A.R.Ş., A.M.T.; Materials – A.R.Ş., A.M.T.; Data collection &/or processing – A.R.Ş., A.M.T.; Analysis and/or interpretation – A.R.Ş., A.M.T.; Literature search – A.R.Ş., A.M.T.; Writing – A.R.Ş.; Critical review – A.R.Ş., A.M.T.

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