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A Retrospective Cohort Study

Hematologic Adverse Effects of Prolonged Piperacillin-Tazobactam Use in Adults

Aysun Benli[1], Serap Şimşek-Yavuz[2], Seniha Başaran[2], Atahan Çağatay[2], Halit Özsüt[2], Haluk Eraksoy[2]

1- Department of Infectious Diseases and Clinical Microbiology, Muş State Hospital, Muş,Turkey

2- Department of Infectious Diseases and Clinical Microbiology, Istanbul Faculty of Medicine, Istanbul University, İstanbul, Turkey

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Address all correspondence to:

Aysun Benli, MD

Department of Infectious Diseases and Clinical Microbiology, Muş State Hospital, Muş, Turkey

Telephone: +90-436-2120670

e-mail: aysunsb@gmail.com

Mobile phone: +905352764175

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Abbreviations:

TZP: Piperacillin-tazobactam
CCI: Charlson's Comorbidity Index
BMI: Body Mass Index
IHEC: Initial higher eosinophil count

Introduction

Piperacillin-tazobactam (TZP) is a broad-spectrum semisynthetic antibiotic. It has increased activity against *Pseudomonas aeruginosa* when compared with other penicillins (1). It is commonly used in nosocomial infections and many other conditions that require broad-spectrum antibiotics, such as febrile neutropenia. Adverse effects of TZP include hypersensitivity reactions, gastrointestinal, renal and hematologic effects. Although most frequently reported hematologic adverse effect of TZP is reversible neutropenia, Coombs-positive hemolytic anemia and thrombocytopenia are also reported (1,2). After observation of fever and neutropenia in some patients who received prolonged TZP therapy, we aimed to find the incidence and risk factors for the development of these adverse effects.

Materials and Methods

Patient selection: Adult patients (aged >18 years) who were given original TZP for more than 10 days at our faculty from January 2013 to December 2014 were included in the study. Usual adult doses were used and TZP was adjusted to renal function, if necessary. Patients with HIV infection and hematologic malignancy; patients with leukopenia and neutropenia; and patients using systemic steroid therapy or chemotherapy within the last 3 months were excluded from the study. If duration between two episodes of TZP therapy exceeded 1 month, episodes were evaluated separately.

Data collection: Patient's informationwasrecorded on previously preparedforms by reviewing medical records.Charlson Comorbidity Index (CCI) was calculated for all patients.

Definitions: Leukopenia was defined as absolute leukocyte count <4000 cells / mm^3, anemia was defined as hemoglobin level <13.5g / dL in males, <12 g / dL in females, or a 2 g decline in patients with low hemoglobin level at the beginning of therapy. Thrombocytopenia

was defined as absolute platelet count <150 000 cells / mm³; neutropenia was defined as absolute neutrophil count <2000 cells / mm³; eosinophilia was defined as absolute eosinophil count ≥ 500 cells / mm³; and hypereosinophilia was defined as absolute eosinophil count ≥ 1500 cells / mm³.

Statistical analysis: Statistical analysis were performed using SPSS version 21. The univariate analyses were investigated using chi-square, Fisher's exact, Student's t-test, and Mann-Whitney U tests, where appropriate. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent risk factors for leukopenia, neutropenia, and eosinophilia. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. $p<0.05$ was considered statistically significant.

Results

One hundred ten TZP therapy episodes of 102 patients included in the study. The epidemiologic, clinical, and laboratorydata of the patients were given in Table 1. Total TZP doseand duration of TZP therapy had no significant effect in development of anemia and thrombocytopenia.However, they were detected as significant risk factors for the development of leukopenia (16.3%), neutropenia (10%), and eosinophilia (10%).

Drug fever appeared in five of the 11 neutropenic patients and in six of the 18 patients with leukopeniawho were afebrile beforehand. All of the patients were alive until the end of the TZP therapy. Therapy was continued with another antibiotic in 8 patients with leukopenia and in 5 patients with neutropenia Body mass index (BMI)was normal in all patients who developed leukopenia and neutropenia.

Characteristics of patients and statistical analysis with and without leukopenia, neutropenia and eosinophilia under TZP therapy are given in Table 2. In the multivariate analysis, lower CCI, lower initial blood leukocyte count, combination of TZP with another

antibiotic, and total duration of TZP therapy were found to be independent risk factors for leukopenia; initial higher blood eosinophil (IHEC) count and >20 days use of TZP were found to be independent risk factors for neutropenia, and IHEC and total duration of TZP therapy were found to be independent risk factors for eosinophilia. The characteristics of leukopenia, neutropenia, and eosinophilia episodes are given separately in Table 3, 4, and 5, respectively.

Discussion

The incidence of leukopenia and neutropenia in patients treated with TZP for more than 10 days were found to be 16.3% and 10% (n=11) respectively in our study. Incidence of neutropenia was found between 0.04% and 34% in previous studies(3-5). The difference between the neutropenia incidence may have resulted from the definitions of neutropenia, duration of TZP therapy and study design. The total dose and duration of TZP therapy were also found the most frequently determined risk factors in the development of these adverse effects in previous studies. (4-6) The mechanisms and reasons of TZP-induced leukopenia or neutropenia have not been clearly determined. It has been shown that TZP causes reversible proliferation arrest in myeloid cells with cumulative doses (7-9).

Duration of TZP therapy was detected as a significant risk factor for the development of leukopenia (21 days), neutropenia (19 days), and eosinophilia (13 days) in our study. Also in a study of 41 patientswith bone-related infections, neutropenia developed in patients who used TZP for more than 18 days (4). In another study that compared risks of neutropenia in patients either treated with TZP or ticarcillin-clavulanate, the risk of neutropenia was higher when children were treated with TZP than with ticarcillin-clavulanate and use of TZP for more than two weeks and this was found to be related with increased risk of neutropenia (5).

In some studies patients who developed neutropenia were found to be younger, as in our study (4,9). However, they could not explainthe mechanismbywhichitdevelops. We could find no other study identifying lower CCI as risk factor for developing leukopenia or

neutropenia during TZP therapy in adult patients. This situationcan be explained by the role ofimmunological mechanisms in the hematologic adverse effects of TZP. Hypersensitivity responsesgivenagainstantimicrobial agentsmay be more effective in youngerpatients withbetterimmune systems and no comorbid conditions. Additionally we found higher initial eosinophil count as another independent risk factor for the development of neutropenia with TZP therapy. Patients with higher eosinophil counts were probably allergic to somethings previously and could be more prone to allergic reactions to antibiotics such as TZP as well; this could also be the reason of neutropenia and leukopenia. In another study, IgG antibodies directed against penicillins and neutrophils were described, the authors concluded that animmune-mediatedpathogenesis was highly probable in developing neutropenia with penicillin use (10).

Combination antibiotic therapy was found to be a risk factor for the development of leukopenia but not neutropenia in our study,it was found as a risk factor also in developing neutropenia in another study (4).Although hematologicadverse effects ofciprofloxacin, which were the most frequently combining agent with TZP in our study, are mildandrarelyseen(11),bone marrowsuppressionassociated with ciprofloxacin usewere shown.Combination antibiotic therapy of TZP should be limited to patients with severe life-threatening *Pseudomonas aeruginosa* infections especially with immunocompromising conditionsbecause of the increased rate of adverse effect, including leukopenia, and lack of evidence of either improved efficacy or decreased resistance (12).

Our study is the first one in some ways; it includes the largest patient sample among studies on the same subject, we evaluated the hematologic adverse effects of TZP as a whole, and finally we analyzed the independent risk factors for development of leukopenia, neutropenia, and eosinophilia.

Conclusion

It should be kept in mind that if TZP therapy is extended more than 2-3 weeks, a patient could develop leukopenia, neutropenia or eosinophilia, especially with combination antibiotic therapy and in younger-aged patients with lower comorbidities. Although consequences of TZP-induced hematologic adverse effects were not devastating, duration of hospital stay after the beginning of TZP were longer in patients with leukopenia and neutropenia. Therefore, especially young patients with lower comorbidities, and patients with IHEC should bemonitored more frequently with complete blood counts.Although combination antibiotic therapy was not found as a risk factor for neutropenia, it was a risk factor for leucopenia and should be avoided unless necessary.

Authorship Contributions

Idea and design: SSY, AB; Acquisition of data: AB, SSY; Analysis and interpretation of findings: SSY, AB, SB, AC, HO, HE; Literature search: AB, SSY, SB, AC, HO, HE; Writing: AB, SSY.

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Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Informed consent was not required due to retrospective study.

Abbreviations

TZP: Piperacillin-tazobactam

CCI: Charlson's Comorbidity Index

BMI: Body Mass Index

IHEC: Initial higher eosinophil count

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Table 1- Characteristics of patients within 110 therapy episodes

Characteristic	Number (%)
Female sex, n (%)	47 (42.7)
Mean age (year) ± mean SD	59.5 ±16
Charlson Comorbidity Index ± mean SD	4.07 ± 2.19
Reason for piperacillin-tazobactam usage	
Lower respiratory tract infections, n (%)	60 (54.5)
Bone and joint infections, n (%)	26 (23.6)
Skin and soft tissue infections, n (%)	18 (16.3)
Other infections, n (%)	6 (5.4)
Mean duration of therapy (day) ± mean SD (total)	21 ± 14
Mean dose of therapy (g) (total)	244 ± 149
Combination antibiotic therapy with, n (%)	63 (57.2)
Ciprofloxacin, n (%)	37 (58.7)
Glycopeptides, n (%)	17 (26.9)

Others, n (%)	9 (14.2)
Leukopenia developed during treatment, n (%)	18 (16.3)
Neutropenia developed during treatment, n (%)	11 (10)
Eosinophilia developed during treatment n (%)	11 (10)
Hypereosinophilia developed during treatment n (%)	1 (0.9)
Anemia developed during treatment, n (%)	21 (19)
Thrombocytopenia developed during treatment, n (%)	7 (6.3)

Table 2-Characteristics of patients with and without leukopenia, neutropenia and eosinophilia

Characteristics	Patients with leukopenia (n=18)	Patients without leukopenia (n=92)	Univariate Analysis p	Multivariate Analysis p (OR, %95 CI)	Patients with neutropenia (n=11)	Patients without neutropenia (n=99)	Univariate Analysis p	Multivariate Analysis p (OR, %95 CI)	Patients with eosinophilia (n=11)	Patients without eosinophilia (n=99)	Univariate Analysis p	Multivariate Analysis p (OR, %95 CI)
Female sex (n)	6	41	0.378		4	43	0.756		4	43	0.756	
Age (mean ± SD)	51 ± 18	60 ± 15	0.071		51 ± 18	60 ± 15	0.137		53.82 ± 18.59	60 ± 15.78	0.252	
Age >40 (n)	13	85	0.026		9	89	0.343		9	89	0.343	
Charlson Comorbidity Index (mean ± SD)	2.89 ± 2.47	4.30 ± 2.07	0.031	0.014 (0.664, 0.478-0.921)	3.09 ± 2.34	4.18 ± 2.16	0.105		3.09 ± 2.07	4.18 ± 2.19	0.124	
Initial leukocyte	8801 ±	13998±	<0.00	0.008	11307±3	13352±6	0.411		12538±	13215±	0.84	

count (cell/mm³)	3143	6148	1	(1.00, 1.00-1.00)	821	249			5320	6167	6	
Initial neutrophil count (cell/mm³)	6101 ± 2601	11093± 5557	<0.001		8612 ±3262	10461±5678	0.397		8950±4575	10423± 5596	0.524	
Initial eosinophil count (cell/mm³)	194 ± 140	118 ± 143	0.011		242 ± 156	118 ± 119	0.012	0.043 (1.004, 1.000-1.008	272 ± 204	115 ± 128	0.002	0.004 (1.006, 1.002-1.087)
TZP therapy duration (day) (mean ± SD)	26 ± 12	20 ± 14	0.001	0.034 (1.047, 1.004-1.092)	26 ± 13	20 ± 14	0.018		30.09 ± 16.61	20.30 ± 13.62	0.002	0.015 (1.047, 1.009 - 1.087)
TZP total dose (gr) (mean ± SD)	320 ± 149	230 ± 145	<0.001		321 ± 162	236 ± 146	0.010		310 ± 150	237 ± 148	0.047	
Total hospital stay after the beginning of TZP (day) (mean ± SD)	51 ± 30	35 ± 37	< 0.001		52 ± 34	36 ± 36	0.015		44.09±21.24	37.38±37.97	0.026	
Combination therapy (n)	16	47	0.004	0.031 (6.58, 1.19-36.	10	53	0.023		8	55	0.350	

				31)						
Ciprofloxacin	11	26	0.007	8	29	0.006		6	31	0.177
Glycopeptides	3	14	0.999	1	16	<0.001		1	16	0.999
TZP therapy duration >14 days (n)	17	69	0.115	10	76	0.450		11	75	0.177
TZP therapy duration >15 days (n)	17	50	0.001	10	57	0.057		10	57	0.048
TZP therapy duration >16 days (n)	16	42	0.001	9	49	0.053		10	48	0.009
TZP therapy duration >17 days (n)	16	40	0.001	9	47	0.048		10	46	0.008
TZP therapy duration >18 days (n)	16	36	<0.001	9	43	0.023		10	42	0.008
TZP therapy duration >19 days (n)	15	32	<0.001	9	38	0.008		9	38	0.007
TZP therapy duration >20 days (n)	15	30	<0.001	9	36	0.007	0.020 (6.84, 1.36 - 34.43)	9	36	0.003

Table 3- Characteristics of the 18 episodes of leukopenia

Sex	Age, year	Time to onset of leukopenia, day	Total dose, g	Initial leukocytes count, $x10^9/L$	Nadir of leukocytes count, $x10^9/L$
F	34	15	180	11.7	2.7
F	76	17	204	5.7	3.7
M	47	10	120	8.9	3.4
F	70	8	96	7.2	3.2
M	46	30	360	13.8	3.2
F	40	15	180	9.8	2.6
M	30	25	300	8.0	3.9
M	69	21	252	7.3	3.2
M	73	21	252	11.8	3.4
M	63	33	396	11.9	3.1
F	60	20	240	6.6	3.4
M	70	29	348	5.2	3.8
M	69	40	480	4.8	3.9
M	22	14	168	6.9	3.1
M	51	20	240	8.0	2.3
M	60	20	240	6.9	3.9
M	32	23	276	6.4	3.8
F	18	21	252	15.9	3.9
Mean ± SD	51.66±18.72	21.22±8.04	254.66±96.48	8.71±3.12	3.36±0.48

Table 4- Characteristics of the 11 episodes of neutropenia

Sex	Age, year	Time to onset of neutropenia,	Total dose, g	Initial neutrophils count, $x10^9/L$	Nadir of neutrophiles count, $x10^9/L$

		day			
M	60	25	300	9.9	0.8
M	47	10	120	6.4	0.5
F	70	8	96	6.2	1.4
M	46	30	360	10.5	1.1
M	73	23	276	9.4	1.2
M	63	24	288	8.1	0.8
F	60	20	240	4.3	1.9
M	51	21	252	3.7	1.3
M	60	23	276	4.5	1.9
F	18	21	252	11.0	1.6
F	19	6	72	9.7	1.5
Mean ± SD	51.54±18.39	19.18±7.7	230.18 ±92.45	7.6±2.68	1.27±0.45

Table 5- Characteristics of the 11 episodes of eosinophilia

Sex	Age, year	Time to onset of eosinophilia, day	Total dose, g	Initial eosinophils count, $x10^9/L$	Nadir of eosinophils count, $x10^9/L$
F	58	1	12	0.3	0.6
M	74	4	24	0.4	0.9
M	65	31	372	0.1	2
F	52	32	384	0.218	1.62
M	30	3	36	0.1	0.7
M	42	7	42	0.748	0.577
M	53	28	336	0.1	1.4
M	74	29	348	0.2	0.5
F	18	3	36	0.126	0.8
M	50	7	84	0.5	0.6
M	76	5	60	0.2	0.5

Mean ± SD	53.81±15.59	13.63±13.12	157.63±16 1.93	0.272±0.204	0.927±0.512