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Original Article

Risk factors for linezolid-associated thrombocytopenia and negative effect of carbapenem combination

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Abstract

Introduction: Linezolid is a synthetic antimicrobial agent with a broad spectrum of activity against virtually all Gram-positive bacteria. Although linezolid is generally well tolerated, the prolonged use of linezolid can lead to myelosuppression, including neutropenia, thrombocytopenia, and anemia. The aim of this study was investigating the risk factors for thrombocytopenia in patients who received linezolid therapy.

Methodology: This retrospective study was performed on patients who received linezolid therapy between July 2007 and December 2017. Thrombocytopenia was defined as either a platelets count of $< 100\times10^9$/L or a 25% reduction from the baseline platelet count.

Results: A total of 371 patients, (198 (53%) male and 173(47%) female were included into the study. Mean duration of therapy was 12.81 ± 5.19 days. Linezolid-induced thrombocytopenia was detected in a total of 111 patients. Using the univariate analysis advanced sex, serum urea concentration, baseline platelet level and low eGFR value were found to be risk factors for linezolid associated thrombocytopenia ($p < 0.05$). According to a multivariate analysis, patients undergoing carbapenem treatment combination therapy ($p = 0.003$) and with a baseline platelet level of $< 200\times10^9$/L ($p = 0.00$) were found to have a high risk of developing thrombocytopenia.

Conclusions: Several factors may influence of linezolid associated thrombocytopenia. Platelet count should be monitored during therapy and thrombocytopenia should be kept in mind in patients with baseline platelet level of $< 200\times10^9$/L, low eGFR, linezolid-carbapenem combination therapy.

Key words: Linezolid; thrombocytopenia; carbapenem.

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Introduction

Linezolid (LZD) is an antibiotic of the oxazolidinone group that inhibits protein synthesis by binding to the ribosomal 50S subunit [1]. It is effective against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE) [2]. As well as having a good tolerability in general, hematologic side effects such as thrombocytopenia (TP) and anemia can be observed with the use of this antibiotic. Although myelosuppression, critical immunity mediated toxicity and vitamin B6 deficiency have been thought to cause TP, its developmental mechanisms are yet to be clearly understood [3]. Non-immune TP usually develops seven to 14 days after the initiation of treatment, whereas immune TP occurs several weeks later [4]. The mechanism of bone marrow suppression, the most common cause of LZD-associated TP development, is usually associated with the dose and duration of treatment, and is not observed within 10–14 days following treatment [5].

Considering pharmacokinetic properties and drug profile, regulation of the dosage of LZD is not recommended in patients with renal insufficiency [2], although there have been studies identifying renal failure as a risk factor in the development of TP [6-8]. A longer course of LZD therapy, chronic liver failure, dose escalation, history of vancomycin use, baseline

thrombocyte level, and low body weight are other reported risk factors in the development of LZD-associated TP [9-14].

The determination of risk factors linked to the development of LZD-associated TP and anemia is important in regards to drug efficacy and the safe use of the drug. In this study, we determine the risk factors involved in the development of TP in patients who underwent parenteral LZD treatment in a tertiary care hospital.

Methodology

This retrospective study was carried out at the Ankara Training and Research Hospital, Ankara, Turkey and involved 473 patients whose data was evaluated and who received parenteral or oral LZD treatment (1200 mg/day), between July 2007 and December 2017. Patients 15 years of age and younger, who had less than five days of treatment, and who had a history of hematologic disease or drug-related TP were excluded from the study. All patients received 1200 mg/day LZD treatment, regardless of body weight or estimated glomerular filtration rates (eGFR). TP was defined as a platelet count of $< 100\times10^9$/L or a 25 percent or more decrease for unexplained reasons in the baseline platelet counts during treatment. Patients with hemoglobin levels < 8 mL/dL at the end of treatment were considered anemic. The patients' records were obtained from the hospital electronic data system, and age, gender, duration of treatment, baseline thrombocyte level, GFR, antibiotics used and hospital admission variables were investigated as risk factors. In order to compare the onset of myelosuppression, patients were divided into three groups based on the duration of LZD treatment: less than seven days; 7–14 days; and 14 days or more. In addition, the patients were further divided into two groups according to the time of TP development: early (≤ 7 days) and late (> 7 days) onset. The patients were also divided into four groups based on their eGFR values: < 10 mL/m^2, 10-50 mL/m^2, 50-90 mL/m^2 and > 90 mL/m^2.

Statistical analyses were carried out using the IBM SPSS Statistics Version 19 program, and the results were expressed as mean values (± standard deviation). Continuous variables were evaluated using a Student's T-test, while categorical variables were evaluated using the χ^2 and Fisher's test. Univariate and multivariate logistic regression analyses were used to determine the likelihood ratio (LR) of the development of LZD-associated TP. A p value of < 0.05 was considered statistically significant.

Table 1. Demographics of patients.

Features	n (%)
Age	63.6 ± 19.4 (15-99)
Sex (F/M)	173/198 (46/54)
Treatments days	12.8 ± 5.19 (5-35)
Chronic Diseases	
DM	70 (18.9)
CRF	62 (16.7)
Cirrhosis	3 (0.8)
CHF	40 (10.8)
Infectious diagnosis	
Pneumonia	221 (59.5)
SSTI	44 (11.8)
Bacteraemia	27 (7.2)
UTI	15 (4.1)
DM food infections	18 (4.3)
CR-BSI	14 (3.7)
Intra-abdominal infections	16 (2.9)
CNS infections	6 (1.6)
Peritonitis	3 (0.8)
Spondylodiscitis	6 (1.6)
Infective endocarditis	1 (0.2)
Isolated microorganisms	
Enterococci	29 (46.8)
MRKNS	19 (30.6)
Streptococcus spp.	6 (9.7)
MRSA	1 (1.6)
Other	7 (11.3)
Total	**371**

DM: Diabetes mellitus, CRF: Chronic renal failure, CHF: Congestive heart failure, SSTI: Skin and soft tissue infections, UTI: Urinary tract infections, CR-BSI: Catheter-related bloodstream infections, CNS: Central nerve system.

Results

A total of 473 patients were evaluated in the study, of which 42 were younger than 15 years, 37 patients had a thrombocyte count of $< 100\times10^9$/L at the beginning of treatment, 22 patients underwent treatment for fewer than five days, and 16 patients had hematologic disease and drug-related TP. All of these patients were excluded from the study. A total of 371 patients (198 of them were males [53%] and 173 of them were females [47%]) were included in the study.

The mean age of the patients was 63.60 ± 19.4 (mean ± standard deviation). The mean duration of LZD treatment was 12.81 ± 5.19 days (5–35). The original LZD preparations were used on 139 (37.5%) patients, while 232 (62.5%) patients used generic drugs. No statistically significant difference was found between the generic drugs and the original molecule in terms of the development of TP ($p > 0.05$). Only 62 (16.7%) patients were treated in line with the culture result, whereas the number of empirically treated patients was 309 (83.3%). No oral LZD treatment was administered to any of the patients. A chronic disease evaluation

demonstrated that 70 patients (19.9%) had diabetes mellitus (DM), 40 (10.2%) had congestive heart failure (CHF), three (0.8%) had cirrhosis and 62 (16.7%) had chronic renal failure (CRF). The basic characteristics, diagnoses and cultured microorganisms of the patients are shown in Table 1.

Patients were divided into three groups according to the duration of LZD treatment. The number of patients undergoing treatment for between 5 and 7 days was 46 (12.3%), between 7 and 14 days was 229 (61.7%) and for more than 14 days was 96 (25.8%). The duration of treatment of LZD was found to have no influence on the development of TP ($p > 0.05$) (Table 2).

The results of the logistic regression analysis revealed no statistically significant relationship between the patient's comorbidity and TP ($p > 0.05$).

TP was detected in 111 (29.9%) of the patients, of which, TP was reported to develop after the seventh day of treatment in 71 patients (63.9%), and within the first seven days of treatment in 40 patients (36.1%), while four (1%) patients were reported to have undergone a treatment change due to TP.

The mean duration of TP development was 7.15 (± 5.68 SD). An evaluation of the patients in terms of the duration of TP development demonstrated that 40 (36.1%) patients developed TP within seven days, whereas the duration was found to be longer than seven days in 71 (63.9%) patients. A baseline platelet level of $< 200\times10^9$/L was found to be associated with the development of TP ($p < 0.001$). During the course of treatment with LZD, the rates of carbapenem, piperacillin, tazobactam and quinolone use, as combination therapy, were found to be 60.4, 19.7 and 3 percent, respectively. Patients undergoing carbapenem treatment for combination therapy were found to have a high risk of developing TP according to a univariate analysis ($p = 0.003$). A low eGFR value was not considered a risk factor for the development TP in patients who were divided into four groups according to their baseline eGFR values ($p > 0.05$) (Table 2). Anemia was detected in 83 (22.4%) of the patients who were undergoing LZD therapy. Anemia as a comorbidity of TP was detected in 28.6% patients, although anemia was not identified as a risk factor for TP ($p < 0.05$) (Table 2). Of the patients who developed TP, 81.3% were being followed up in the intensive care unit. The mortality rate was reported as 71.3% among patients who developed TP while undergoing LZD therapy, and this rate was 27.1% in patients without TP ($p < 0.001$). Bleeding was not the cause of death of any

Table 2. Risk factors for thrombocytopenia.

	TP N = 111 (29.9%)	**Not TP N = 260 (70.1%)**	**p**	**Odds ratio**	**95%Cl**	**p**
Age	64.5 ± 19.3 (16-99)	63.21 ± 19.55 (15-92)	0.649			
Sex (F/M)	39/**72** (35. 64)	134/126 (48/52)	**0.004**	1.912	1.203-3.201	**0.007**
Treatments days	12.57 ± 4.53 (5-28)	12.91 ± 5.45 (5-35)	0.561			
5-7 days	14 (12.6)	32 (12.3)				
7-14 days	66 (59.5)	163 (62.7)				
> 14 days	31 (27.9)	65 (25)				
Laboratory values at the beginning of treatment						
Hemoglobin	10.17 ± 2.13	10.17 ± 1.95	0.647			
Platelet	200846 ± 70923 (101000-474000)	292346 ± 118494 (110000-810000)	**< 0.00**	2.81	2.747-8.778	**< 0.001**
Urea	60.57 ± 48.4	74.27 ± 66.1	**0.486**	0.999	0.994-1.004	0.771
Creatine	1.85 ± 1.9 (0.2-9.09)	2.26 ± 5.3 (0.3-74)	0.534			
eGFR	60.57 ± 48.4(3.21-285)	66.05 ± 45.11 (2.25-245)	**0.176**	1	0.993-	0.923
1	7 (6.3)	17 (6.5)				
2	23 (20.7)	45 (17.3)				
3	24 (21.6)	33 (12.7)				
4	57 (51.4)	165 (63.5)				
Combined antibiotics						
Carbapenem	80 (72.1)	144 (55.5)	**0.003**	1.937	1.176-3.191	**0.009**
Glycopeptides	7 (6.3)	9 (3.5)	**0.218**	1.095	0.357-3.356	0.874
Quinolones	5 (4.5)	6(2.3)	**0.255**	1.356	0.367-5.010	0.648
Piperacillin-tazobactam	24 (21.6)	49 (18.8)	0.539			

patient. Although statistically significant, TP was not the cause of death in any of the patients.

Discussion

An increase in resistant bacterial strains is associated with increased LZD use, particularly in intensive care units. LZD is used as an important treatment agent for healthcare-associated pneumonia that develops due to Gram-positive resistant pathogens, in the absence of other agents for various reasons or when treatment is inadequate. It is usually well tolerated when used with caution, despite its potential toxicity, reversible bone marrow suppression, and the risk of developing TP and anemia [15]. The rate of TP development associated with LZD therapy varies between 16.7% and 60.5% [16-18], although these rates vary from country to country, and may be due to ethnic differences. The rate of LZD associated TP was 27.5% in the present study. The mean time of development of TP in patients was 8.49 days. A total of 49 (62.8%) patients developed TP after seven days of treatment. Although the mechanism behind TP development under LZD therapy is not clear, myelosuppression, which is the most common cause, usually develops on the 7thor 14th day of treatment [5], but late onset TP development was more frequent in our patients. LZD treatment is thought to cause temporary TP by leading to myelosuppression [19]. Literature review demonstrated that the development of TP was not immune related.

There have been many studies identifying LZD therapy of ≥ 14 days as the main risk factor for TP [20-24], although it has been suggested that a prolonged treatment is not associated with the development of TP [21]. No statistically significant relationship has been identified between the duration of treatment and TP development in the present study. Around 61.3% of our patients received LZD treatment for 7–14 days, while 26.5% of the patients underwent treatment of ≥ 14 days. We thought that long-term treatment is not considered a risk factor for LZD associated TP due to the large number of patients in our study with treatment durations of between 7 and 14 days.

We found that the administration of carbamazepine in combination with LZD treatment increased the risk of developing TP with a baseline platelet count of < 200×10^9/L. A combination of LZD therapy with quinolones, prolonged treatment duration and renal failure have been shown by many studies to pose a risk for the development of TP (6-8, 14-17, 20). Carbapenem can rarely cause anemia, TP and prolonged bleeding time [21]. In this study, we also found that undergoing combination therapy of LZD with meropenem increased the risk of TP development ($p = 0.009$; LR, 1.93; 95% CI, 1.17-3.19). In a study evaluating drug related TP on intensive care unit patients, antibiotics including quinolone, vancomycin, broad spectrum β-lactamases and carbapenem, or drugs such as non-steroidal anti-inflammatory agents, anticonvulsants, antiplatelet agents and heparin, were identified as risk factors. In that study, however, LZD was not among the investigated antibiotics and combination therapies were not discussed [18]. Similar to the present study, Chen *et al*. [22] demonstrated that the use of levofloxacin, caspofungin, and meropenem was a risk factor for the development of TP in patients receiving LZD. In the present study, we found that a combination of piperacillin and tazobactam, which are included in the β-lactam group and are known to cause TP, was not a risk factor for TP. Empirical carbapenem treatments are initiated more often, considering the resistance profile of the intensive care units in our hospital. It was an anticipated finding that the number of patients receiving carbapenem and LZD combination therapy in the intensive care units of our hospital would be higher than other combination therapies. Other antibiotics were not identified as risk factors for LZD-associated TP, which may be attributed to the small number of patients treated with other β-lactamase and quinolones.

Impaired renal function was identified as an independent risk factor for MRSA and VRE infections [23], and LZD is considered as a treatment option in such cases. In a study by Hanai *et al*. [24], the risk of LZD-associated TP was found to increase 2-, 8- and 9-fold in cases of mild, moderate and severe renal insufficiency, respectively. Studies have shown that the risk of LZD-associated TP increases when creatinine clearance (CLcr) is less than 30 mL/min [25,26], although in these studies, the sample size was found to be small and the level of renal insufficiency of the patients was not evaluated. In their study of 43 patients, Ichie *et al*. [20] did not identify renal insufficiency as a risk factor for LZD associated TP, while in the present study, no significant difference was noted in the risk of TP development between hemodialysis patients with eGFR values of ≤ 50 μg/mL and patients with normal renal function. An evaluation of the baseline platelet count in patients with renal insufficiency and hemodialysis suggests that LZD therapy could be given with a close follow-up. In a further study, a blood concentration target suitable for renal function was determined to reduce the development of LZD-associated TP, with a safe target range specified as

Cmin 3.6-8.2 μg/mL. Baseline and maintenance LZD doses were determined using a formula based on the patient's CLcrs [27]. It has also been suggested that the administration of LZD doses in excess of 22 mg/kg is a risk factor for TP, and that the risk of TP increases in the presence of renal insufficiency and a low pre-treatment platelet count [17]. In our study, we were unable to determine the blood concentrations of LZD of the patients, and so a standard dose was given to each patient. LZD is metabolized by non-enzymatic oxidation, and 30–40 percent of it is excreted through the urine without change [28-30]. Although formulations have been developed, it should not be forgotten that there is as yet no guideline on LZD dose adjustments in patients with renal insufficiency.

Previous studies have demonstrated a relationship between the baseline platelet level of LZD therapy and the development of TP [22,31,32]. In the study by Grau *et al*. [21], a baseline platelets' count of $\leq 240\times10^9$/L was determined as a risk for the development of TP, while a figure of $\leq 181\times10^9$/L was identified in the study by Chen *et al*. [31]. Similar to other studies evaluating baseline platelet levels, we also identified the baseline platelet value as risk factor. A value that is not normally considered as TP is $\leq 200\times10^9$/L, which was found to be a risk factor for LZD associated TP in our study ($p < 0.001$; LR, 2.81; 95% CI, 2.74-8.77). Accordingly, patients with a baseline platelet level of $\leq 200\times10^9$/L during treatment should be closely monitored for TP.

Conclusion

In the present study, a baseline platelets' count of $\leq 200\times10^9$/L, male gender, and an LZD-meropenem treatment combination were identified as risk factors for LZD associated TP. Although many studies have shown that prolonged treatment with LZD and renal failure are the main risk factors, we were unable to identify them as risk factors in the present study.

We recommend that care should be taken to reduce the risk of LZD associated TP in patients that present with these risk factors.

Limitations of the study

Some limitations were identified in our study. Firstly, the plasma concentrations of LZD of our patients were not investigated. Secondly, the study was conducted retrospectively. Finally, the ratio of LZD and carbapenem combination was higher than the other combinations due to the resistance profile of our hospital. As a result, there is a need for prospective studies to be carried out that take these limitations into account.

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