LINEZOLID INDUCED THROMBOCYTOPENIA IN A PATIENT WITH RENAL INSUFFICIENCY: A CASE REPORT AND A RESTROSPECTIVE CASE STUDY

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Background

Linezolid is a new antimicrobial agent with a broad spectrum of activity against all clinically important Gram-positive bacteria, including methicillin-resistant staphylococcus aureus and vancomycin-resistant enterococci (VRE).[1] The dosage of the incidence of linezolid-induced thrombocytopenia was reported 2.4% in phase III trials. The clearance of Linezolid is not altered in patients with renal insufficiency and no dose adjustment is necessary.[2] Therefore, linezolid is a suitable and reasonable drug of choice for the patients with renal insufficiency who have MRSA or VRE infection. Moreover, Renal insufficiency is also known to cause thrombocytopenia.

Purpose

This study is to investigate if the incidence of Linezolid-induced thrombocytopenia in the patient with renal insufficiency was higher than others with normal renal function.

Materials and Methods

The case report is in relation to severe thrombocytopenia (platelet count <100x10^9 platelets/L) in a patient with hemodialysis who was treated with linezolid for VRE infection. The literature review was done based on the steps of evidence-base medicine and searched in Cochran Library, ACP J Club, Clinical Evidence and Pub Med until Aug 2015. The search key words were linezolid and thrombocytopenia.

Then, a retrospective study was performed in the patients treated with linezolid and been evaluated with the incidence of linezolid-induced thrombocytopenia. All patients had gram-positive bacterial infections.

Case report

A 84-year-old female, with a history of diabetes mellitus type2, congestive heart failure, hypertension, dementia and end stage renal disease with regular hemodialysis was admitted to our hospital for lower abdomen pain, dysuria and suspect sepsis in May 14, 2015. Although chest X-ray showed no any obvious pneumonia, mild elevated CRP (33.8ug/ml) was found. Empiric antibiotic therapy was started immediately with ceftazidime. After 12 days of hospitalization, her clinical condition worsened and she was transferred to the intensive care unit (ICU) because of hypovolemic shock. During the days of her ICU stay, intermittent fever attacked. Under the impression of blood stream infection, vancomycin was added on with ceftazidime for infection control. Multiple-drug resistant enterococci was insolated in blood cultures (**Table 1**). Physician prescribed linezolid 600mg twice per day for treatment according the report of antimicrobial susceptibility test. After 7 days of linezolid therapy, her platelet count decreased from 154x10^9/L to 87x10^9/L. Linezolid administration was discontinued based on the resolution of the underlying infection and the complete course of 14 days (**Figure 1**). Normal platelet count (up to 272x10^9/L) was reached after 11days of linezolid withdrawal.

Table 1 The report of blood culture

Sample Source: Blood			Collection Date: 2015/05/25		
◆ Organism isolated: 1.Gram Positive Coccus 2.Enterococcus casseliflavus					
◆ Antimicrobial susceptibility test					
Clindamycin	R	(≥8)	Erythromycin	R	(≥8)
Trimethoprim/Sulfamethoxazole	R	(≥320)	Ampicillin-sulbactam	R	(≥32)
Vancomycin	R	(≥32)	Gentamicin (high level)	S	
Tigecycline	S	(≤0.12)	Moxifloxacin	R	(≥8)
Streptomycin (high level)	R		Teicoplanin	R	(≥32)
Linezolid	S	(1)	Tetracycline	R	(≥16)

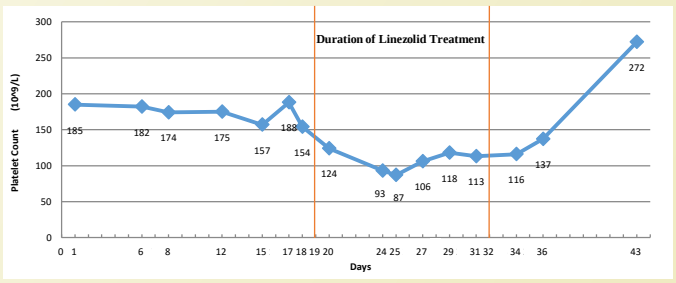

Figure 1 Platelet count trend during patient hospital stay

Results

An increasing number of clinical studies in the literature suggest a correlation between the linezolid-induced thrombocytopenia and renal dysfunction. Lin et al. published a retrospective case-control study compared the tolerability and efficacy of linezolid between patients with and without renal insufficiency in 2006. The incidence of severe thrombocytopenia in 62 patients was significantly more common in patients with renal insufficiency (64.7% vs. 35.6%; P=0.039).[3] Also Takahashi et al. found that the time to the onset of thrombocytopenia in patients with creatinine clearance <50 mL/min was significantly shorter than that in patients with creatinine clearance ≥50 mL/min (6.7 ± 4.4 and 8.5 ± 5.2 days, P = 0.039). Thrombocytopenia occurred in 128 of 331 patients (38.7%) in this study and oral administration of linezolid decreased the risk of thrombocytopenia than parenteral administration (OR 0.38, 95% CI 0.15–0.97, P = 0.042). This suggests dose adjustment may be required in at-risk patients, especially those with renal dysfunction.[4] Cossu et reported a case of a patient with acute kidney injury had severe thrombocytopenia after 10 days treatment and suggest that clinicians should consider the potential risk of this complication, especially in elderly patients with end-stage renal disease.[5]

In our study, sixteen patients (10 female) with mean age of 64.8 years were enrolled and treated at Kaohsiung Municipal Hsiaokang Hospital between Aug 2014 to Aug 2015 (**Table 2**). The samples size was not much because of the linezolid-using limitation by the national healthy insurance of Taiwan. Because the formula-derived estimated of renal function, such as the that proposed by Cockroft and Gault, have not been validated in the elderly population. The study used gender-specific cut-off values (serum creatinine > 1.3mg/dl in women and > 1.5mg/dL in men) to characterize renal impairment.[6] 3 of 16 cases were excluded because of one day therapy with linezolid and no serum lab data after linezolid treatment. At the start of linezolid treatment, 7 patients (53.8%) had impaired renal function. After treatment, Six patients were with decreased platelet count over 25% from baseline in the period of linezolid treatment and four of them (67%) were with renal insufficiency (**Figure2**). Two patients with renal insufficiency had severe thrombocytopenia. Although the result doesn't show significant, the incidence of thrombocytopenia seems more common in patients with renal insufficiency (57% vs 33%, p=0.175). This may due to the small sample size.

Conclusions

The study result showed the incidence of linezolid-induced thrombocytopenia was higher in patients with renal insufficiency. Clinicians should consider the potential risk of linezolid treatment and close monitor the platelet count in the patients with renal insufficiency. Further studies should be encouraged to determine if the dose adjustment of linezolid for renal insufficiency is necessary for reduced the incidence of linezolid-related thrombocytopenia.

Table 2 Demographic and clinical characteristics of patients

Characteristic	Data
Age (years), mean±SD	68.3±15.0
Range	45-95
Gender (male/female)	4/9
Body weight(kg), mean±SD	54.7±12.5
Range	40.5-78.0
Baseline platelet counts (×10^9/L), mean±SD	335.6±147.4
Range	110-641
Duration of therapy (days), mean±SD	10.9±5.1
Range	3-21

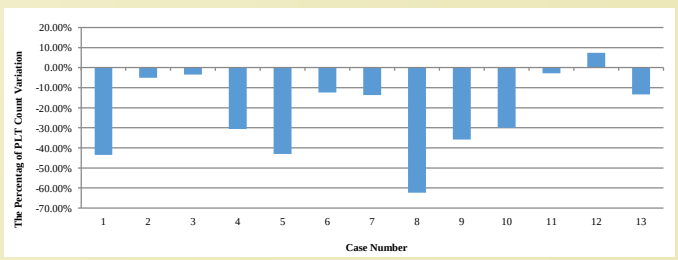

Figure 2 The percentage of platelet count variation for each case

Reference:

1. *Clin Infect Dis* 2006;42:66-72
2. *Eur J Clin Pharmacol* 2014;70:23-8
3. *Int J Antimicrob Agents* 2006;28:345-51
4. *J Infect chemother* 2011;17:382-7
5. *Int J Antimicrob Agents* 2014;44:242-7
6. *Kidney Int 1999;55:1878-8*