

## **Occurrence of linezolid induced thrombocytopenia and its association with the risk factors: a review article**

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### **ABSTRACT**

Linezolid is the oxazolidinone group of antibiotic with wide range of activity against the gram positive bacteria including methicillin resistant staphylococcus aureus and penicillin resistant pneumococci and vancomycin resistant enterococci. Patients who are on linezolid were reported to have reversible myelosuppression especially thrombocytopenia and anaemia. Since there are less number of studies regarding the occurrence of thrombocytopenia and the risk factors associated with it, this study was undertaken to evaluate the occurrence of linezolid induced thrombocytopenia and its association with risk factors. It was a systematic review with synthesis of available literature in English language. Articles were retrieved using search terms included “linezolid”, “and”, “or”, “thrombocytopenia” from Clinical key and PubMed, published during 2000 - 2017. Out of 16 studies retrieved, only 7 studies were analysed based on inclusion and exclusion criteria; of them, 3 were found to be prospective and retrospective cohort each and only one was retrospective cross-sectional study. The occurrence of linezolid induced thrombocytopenia range from 18-50% with normal renal function and 57% of incidence associated with renal insufficiency patients. The risk factors were found to be dose of linezolid >18-27mg/kg, body weight of subjects <55kg, creatinine clearance <88.39 to 60ml/min/1.73m<sup>2</sup> and baseline platelet count <200\*10<sup>3</sup>/mm<sup>3</sup>, serum albumin concentration, serum creatinine, concomitant caspofungin therapy and duration of linezolid therapy.

**Keywords:** Baseline platelet count, Linezolid, Occurrence, Oxazolidinone, Risk factors, Thrombocytopenia

### **INTRODUCTION**

Linezolid is the Oxazolidinone group of antibacterial agent with wide range of activity against the gram positive bacteria including Methicillin Resistant Staphylococcus Aureus (MRSA) and penicillin resistant pneumococci and vancomycin resistant enterococci.<sup>1</sup> It disrupts bacterial growth by inhibiting the initiation process of protein synthesis by binding to domain V of the 23S ribosomal RNA of the 50S subunit of bacterial ribosomes.<sup>2,3</sup> Linezolid site of inhibition occurs earlier in the initiation

process than other protein synthesis inhibitors like chloramphenicol, clindamycin, aminoglycosides and macrolides that interfere with the elongation process.<sup>4</sup> The site of inhibition is specific to linezolid, so cross-resistance to other protein synthesis inhibitors has not yet been reported. It may also suppress virulence factor expression and decrease toxin production in gram-positive pathogens.<sup>5</sup> It has 100% bioavailability by oral because it has high water solubility and robust tissue penetration.<sup>6</sup> It is metabolized by liver into two primary oxidation products and 80% of the drug was excreted through kidney and 20% in the feces respectively.<sup>7,8</sup> It's half-life

approximates 5-7 hrs and the dosing interval is 12 hrs.<sup>9</sup> Patients who are on treatment with linezolid were reported to have reversible myelosuppression, especially thrombocytopenia and anaemia. Thrombocytopenia has the highest incidence of 30% and anaemia with 2.8-47.3% among patients receiving linezolid.<sup>10</sup> The risk factors for linezolid treatment are thrombocytopenia, renal insufficiency, chronic liver disease, respiratory tract infection, duration of linezolid therapy, baseline platelet count, low body weight and the use of vancomycin.<sup>11</sup> Hence, patients should be observed for myelosuppression during linezolid treatment because it can occasionally result in discontinuing the treatment.<sup>12</sup> As there were limited studies in this regard, we sought to review and evaluate the occurrence of linezolid induced thrombocytopenia and the associated risk factors.

## REVIEW OF LITERATURE

### Search strategy

Authors carried out a systematic review with synthesis of available literature in English language. Articles were retrieved using search terms included “linezolid”, “and”, “or” “thrombocytopenia” from Clinical key and PubMed published from 2000 to 2017. Out of 16 studies retrieved, only 7 studies were analysed based on inclusion and exclusion criteria; of which 3 each were prospective and retrospective cohort and only one was retrospective cross sectional study.

### Inclusion criteria

Authors have included the studies in which patients aged  $\geq 18$  years and on linezolid therapy more than 3 days.

### Exclusion criteria

Studies included patients who had severe thrombocytopenia ( $<50 \times 10^9/L$ ) before linezolid treatment, bleeding disorder, known liver disease, coagulopathies, on any anticancer drugs during linezolid therapy, platelet count not recorded before or after linezolid therapy, suffering from cancer, missed clinical data and case reports were excluded.

### Data extraction

Authors discarded irrelevant studies after screening all titles and abstracts and evaluated the full texts of the remaining studies to determine the inclusion and exclusion criteria.

The entire selection process is summarized in the PRISMA flow chart (Figure 1). Demographic, epidemiological, clinical variables were collected in detail including epidemiological design of the study, location of the study, age of the enrolled patients, dose and duration of the drug, baseline platelet count, creatinine clearance, the risk

factors associated with thrombocytopenia and occurrence of thrombocytopenia.

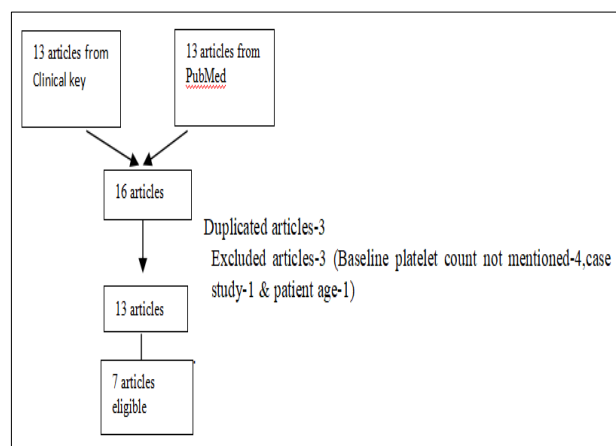


Figure 1: Study flow chart.

## DISCUSSION

Out of total seven articles reviewed; four studies were performed in Japan, two in China, one each in Taiwan and Italy. Thrombocytopenia definition used varied among the studies; thrombocytopenia is considered, if there was  $>25\%$  reduction from the baseline platelet count with final platelet count  $<1$  lakh/ $\text{mm}^3$ ,  $>25\%$  reduction from the baseline platelet count only;  $>30\%$  from the baseline platelet count;  $>50\%$  from the baseline platelet count (Table 1).<sup>1,6,11,13-15</sup>

Two studies which defined thrombocytopenia as  $>25\%$  reduction from the baseline platelet count and final platelet count  $<1$  lakh/ $\text{mm}^3$  has shown the occurrence ranging from 18 - 48% with mean age range of 66 to 83 years with mean dose of 24mg/kg in one study and 600 mg BD in other study and mean duration of 12 to 14 days.<sup>1,13</sup> Another two studies with thrombocytopenia definition  $>25\%$  reduction from the baseline platelet count showed the occurrence of about 16.6-50% with mean age of 50-61 years with a mean dose of 17-20mg/kg in one study and 600mg BD in another study for mean duration of 8 days -12 weeks.<sup>11,15</sup>

Study with definition of thrombocytopenia  $>30\%$  from the baseline platelet count showed occurrence of 48.4% with mean age range of 61-67 years with mean dose of 21mg/kg with mean duration of 11-16 days.<sup>7</sup>

Study which has considered thrombocytopenia  $>50\%$  from the baseline platelet count in another study, had an occurrence of 48% with mean age range of 61-67 years, mean dose of 19-23mg/kg and median duration of 14 days.<sup>6</sup> In one study where the thrombocytopenia occurrence has been analysed based on presence or absence of renal insufficiency showed 57% and 33% with and without renal insufficiency with mean age of 68 years with dose of 600mg BD and mean duration of 10 days.<sup>14</sup>

**Table 1: Characteristics of the studies.**

Authors and Place of study	Type of study and Sample size (N)	Thrombocytopenia (TP) definition	With/without TP	Age (mean) years	Number of subjects (N)	Dose of linezolid (Mean±SD) mg/kg body wt.	Duration of linezolid (Mean) day/week	Occurrence (percentage)	Baseline platelet count (10 <sup>3</sup> /mm <sup>3</sup> )	CrCl (ml/min)
Niwa.T et al <sup>1</sup> Japan	Prospective 50	>25% and <1lakh/mm <sup>3</sup>	With TP	66	9	24.3±2.1	12 days	18%	179±96	64.5±60.4
			Without TP	62	41	20.4±4.2	12 days		274±143	103.6±89.0
Chen.C et al <sup>11</sup> China	Retrospective 254	>25% reduction in baseline	With TP	61.36	69	19.99±4.18	10.31±5.64 days	50%	212.5±76.96	87.67±59
			Without TP	56.83	185	17.83±4.39	8.55±5.54 days		224.71±72.85	106.90±58.28
Bi L.et al <sup>13</sup> China	Retrospective 50	>25% and <1lakh/mm <sup>3</sup>	With TP	83±9	24	600mg BD*	14±2 days	48%	204±118	46±36
			Without TP	80±11	26	600mg BD*	12±2 days		272±101	60±43
Garazzino S et al <sup>15</sup> Italy	Prospective 31	>25% reduction in baseline	With TP	50.5	2	600mg BD*	12 weeks	16.6%	220	
			Without TP		29	600mg BD*				
Natsumoto B et al <sup>6</sup> Japan	Retrospective 101	>50% reduction in baseline	With TP	67.83	42	23.47±5.1	14(3-67) days**	48%	289.98	67.2±41.57
			Without TP	61.76	59	19.9±5.3	14(1-63) days**		249.63	181.85±156.9
Hanai Y et al <sup>7</sup> Japan	Retrospective 221	>30% reduction in baseline	With TP	67.6±13.1	107	21.8±2.4	16.0±13.6 days	48.4%	239.8±133.2	35±24.3
			Without TP	61.7±15.2	114	21.0±2.3	11.6±6.9 days		239.0±140.0	78.4±36.4
Wu H et al <sup>14</sup> Taiwan	Prospective 13	>25% reduction in baseline	With TP	68.3±15.0	6	600mg BD*	10.9±5.1 days	33% in normal renal function 57% in renal pts	335.6±147.4	Not given

TP-thrombocytopenia

\*Standard dose was administered; \*\* Median duration of linezolid was documented instead of mean

**Table 2: Characteristics of risk factors in this study.**

Studies	Baseline platelet count (<200*10 <sup>3</sup> /mm <sup>3</sup> )	Creatinine clearance (ml/min)	Hemo-dialysis	Dose mg/kg	Body weight (<55kg)	Duration (days)	Serum albumin (g/l)	Caspofungin	Serum creatinine (mg/dl)
Niwa T et al <sup>1</sup>	OR - 24.9 p - 0.024			>22 O - 9.55 p - 0.010	OR - 33.2 p - 0.012				
Chen C et al <sup>11</sup>	NA	OR - 0.10 p - 0.04		>18 OR - 1.12 p - 0.001		NA	OR - 0.95 p - 0.03	OR - 2.81 p - 0.01	
Natsumato B et al <sup>6</sup>				>20 Adjusted OR - 1.14 p - 0.0026					Adjusted OR - 1.51 p - 0.04
Hanai Y et al <sup>7</sup>		Crcl -52.2 Adjusted OR - 0.94 p - 0.001	Adjusted OR - 3.32 p - 0.011			14.7 days Adjusted OR - 1.14 p - 0.001			

OR - odd's ratio; NA- Not available; p - p value

Among seven studies, only four have evaluated risk factors for linezolid induced thrombocytopenia (Table 2), in one study by Natsumoto et al, serum creatinine and Dose Per Kg bodyweight per Day (DPKD, mg/kg/day) has been identified as risk factor.<sup>1,6,7,11</sup> The adjusted odds ratio with 95% confidence interval for serum creatinine (mg/dl) and DPKD, were 1.51 (1.01-2.50) and 1.14 (1.05-1.26) respectively by Bi and multivariate logistic regression.

In a study conducted by Hanai Y et al, multiple logistic regression analysis identified creatinine clearance (CrCl), hemodialysis and duration of linezolid therapy with adjusted odds ratio (OR) of 0.94 (0.92-0.95,  $p < 0.001$ ), 3.32 (1.14-9.67,  $p < 0.011$ ) and 1.14 (1.07-1.21,  $p < 0.001$ ) respectively with 95% CI as the risk factors for linezolid induced thrombocytopenia. It was found that the incidence of thrombocytopenia was less (9.1%) in normal subjects compared to renal insufficiency subjects (18.5 - 81.4%), the discontinuation rate was higher in renal insufficiency compared (7.4%-62.5%) to normal subjects (2.3%) and the onset of thrombocytopenia ranging from 7-12 days.<sup>7</sup> It was also observed that the incidence of anaemia was 8.6 - 43.5% with linezolid duration ranged from 7-10 days and there was no discontinuation of the therapy due to anaemia.

Study by Niwa et al, depicts daily dose  $>22\text{mg/kg}$  and body weight  $<55\text{kg}$  with odds ratio (OR) of 9.55 with 95% CI (1.72-53.1,  $p < 0.010$ ) and baseline platelet count of  $<20 \times 10^3/\text{mm}^3$  with OR of 6.20 (1.30-29.5,  $p < 0.022$ ) respectively as risk factors by univariate logistic regression and they also observed that dose adjustment of linezolid with one of the risk factor had prolonged onset of thrombocytopenia without affecting efficacy.<sup>1</sup> The occurrence of thrombocytopenia increased from 18-72% when the DPKD and body weight of the patients increased from  $<17$  to  $>27\text{mg/kg}$  and  $>70\text{kg}$  to  $<45\text{kg}$  respectively.

In retrospective cross-sectional Chen c et al study, creatinine clearance (OR-0.99), serum albumin concentration, daily dosage and caspofungin therapy were the risk factors by using multivariate logistic regression analysis and ROC curves.<sup>11</sup>

Few studies have reported that the mean area under the blood concentration time curve (AUC) of linezolid is high in  $>80\text{yr}$  old patient and bodyweight  $<40\text{kg}$  ( $811.3\mu\text{ghr/ml}$ ) when compared to  $<80\text{yr}$  and bodyweight  $>40\text{kg}$  ( $217.6\mu\text{ghr/ml}$ ).<sup>10</sup> Further prevalence was 63.6% in AUC  $>800\mu\text{g-hr/ml}$  and 51.3% in AUC  $<800\mu\text{ghr/ml}$ .<sup>6</sup> Dong et al reported that high plasma concentration of linezolid is a risk factor.<sup>11</sup> Very limited studies were available, so further studies should be conducted to evaluate the risk factors associated with linezolid induced thrombocytopenia with respect to drug-drug interactions with linezolid and association between the linezolid plasma concentration and occurrence of thrombocytopenia.

The strength of the study was inclusion of both prospective and retrospective studies in-terms of evidence, gives good results and less bias. Study was unique in terms of the attempts made to draw some conclusion and evidence on the occurrence and the factors associated with it. Unfortunately, it was not possible to perform meta-analysis because of high level of heterogeneity ( $I^2 = 48\%$ ) among the selected articles.

The limitations of the study were; power of the study was not mentioned in any of the articles, only English language articles were included, the definition of thrombocytopenia was different in each article & lastly, a limited number of studies were available for the review.

## CONCLUSION

The occurrence of linezolid induced thrombocytopenia ranged from 18-50% and the associated risk factors were low creatinine clearance, hemodialysis, body weight  $<55\text{kg}$ , increase DPKD low baseline platelet count, increased serum creatinine, increased duration of linezolid therapy, serum albumin concentration and concomitant caspofungin therapy. Hence, adequate and frequent monitoring for blood counts is essential in patients on linezolid therapy.

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