Original Research Article

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Association between serum linezolid concentration and haematological toxic effects: a longitudinal study

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ABSTRACT

Background: Linezolid is a commonly used antibiotic and reported various drug related adverse effects mainly haematological toxicity like thrombocytopenia, leukopenia and anaemia. But a significant association between linezolid plasma concentration and drug related adverse effects are not documented yet. This longitudinal observational study aims to study the incidence of drug related haematological toxicities and its association with serum Linezolid concentration and also evaluate the clinical outcome.

Methods: After obtaining informed consent, each patient (18-50years) was given linezolid (600mg/12hourly), and evaluated for haematological (haemoglobin, platelets, WBCs), renal (as serum creatinine), and hepatic (as serum transaminases status), together with an assessment of drug C min values. These evaluations were repeated once a week or in concomitance with the development of an adverse event up to the end of linezolid therapy. The parametric dependent 't' test was applied (p<0.05) and normality of data were performed by Kolmogorov Smirnov test, follows normal distribution.

Results: There was significant reduction in platelet count and haemoglobin value seen from baseline till end of treatment (p<0.001) and there was 13% reduction in WBC count in all patients on day 14 when compared to baseline (p<0.001) indicating haematological toxicity according to WHO toxicity grading scale. All the patients (n=8; 26.6%) who developed drug related haematological toxicity also showed comparable increase in plasma linezolid concentration (C min) >10 mg/L at the end of 14 days.

Conclusions: The capability to monitor plasma linezolid concentration (C min; trough value) once a week may lead to a significant improvement in clinical use of the drug both in terms of efficacy and tolerability as the study observed that there is association between linezolid concentration and risk of developing drug related haematological toxicity.

Keywords: Adverse effects, Gram positive infection, Haematological toxicity, Linezolid, Plasma trough concentration, Safety outcome

INTRODUCTION

Most of blood stream infections in critically ill patients are caused by gram positive bacteria mainly multidrug resistant strains viz, methicillin-resistant staphylococcus

aureus (MRSA), vancomycin resistant staphylococcal aureus(VRSA), vancomycin resistant enterococci (VRE) which are common cause of nosocomial, community acquired infections. Linezolid (LNZ) is an oxazolidinone antibiotic characterised by a broad spectrum of activity

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against gram-positive micro-organisms resistant to betalactams and glycopeptides and whose use has been increased in recent years.² pharmacokinetic and pharmacodynamic of linezolid have been extensively studied in healthy volunteers and in patients with gram positive bacterial infections.³ A most favourable antibacterial effect is seen when plasma drug minimum concentration are above inhibitory concentration (MIC) till the end of treatment and the ratio between the area under curve (AUC) and MIC is greater than 100, because of its intrinsic chemico-physical characteristics and high bioavailability, it is assumed that adequate serum linezolid concentration will be achieved when using recommended dose of 600mg/12 hourly.^{2,3}

The FDA has approved linezolid therapy in the year 2000 and it can be used safely for 28 days, beyond this may lead to high plasma concentration and an increased risk of non-negligible toxicities.^{4,5} As a consequence, increased drug concentrations could represent a risk factor for severe toxic effects against target organs (e.g. brain, optic nerve, kidney, skeletal muscular tissue) leading to increased risk of severe adverse reactions thrombocytopenia, myelosuppression mainly peripheral neuropathy.^{6,7} No studies have documented the intra-individual variability which is mandatory prerequisite for the feasible application of therapeutic drug monitoring (TDM). The capability to monitor TDM plasma linezolid concentration may lead to a significant improvement in clinical use of the drug both in terms of efficacy and tolerability and even decrease in development of drug resistance.

Zoller M et al say wide inter-individual variability in linezolid C min values were found in patients on LNZ. Elevated LNZ plasma trough concentrations (C min values) have been reported in patients with renal or hepatic dysfunction, critically ill patients, renal transplant cases who experienced thrombocytopenia after starting treatment with linezolid compared with values measured in healthy volunteers. The rate of therapy failure and adverse effects may be in part explained by a high variability of linezolid serum concentration in patients.

However, it is clearly not mentioned the relative frequency of linezolid therapy and how often the laboratory or clinical monitoring for drug toxicity should be performed and the safer upper threshold level for linezolid plasma C min has not vet been conclusively defined. If any correlation between LNZ concentration and the risk of developing drug related haematological toxicity is observed then the application of therapeutic drug monitoring may improve the safety outcome of patients receiving LNZ therapy but there is no enough evidence that the application of monitoring only in those patients who are prone to individual pharmacokinetic variability will still need to be investigated. So, study was planned with the objective to assess the association between serum linezolid concentrations haematological toxic effects and to find whether early

measurement of plasma linezolid concentrations (first week after starting treatment) can predicts subsequent development of drug-related side effects and also to assess the clinical outcome (efficacy) and safety of linezolid.

METHODS

This is a longitudinal study conducted in an institution of medical education and tertiary care centre in Karnataka. India. The study was approved by Institutional Ethics Committee for Humans. The patients of 18-50 years of age group included in this observational study were those admitted in surgical wards, who were treated intravenously or orally with linezolid at the standard daily dosage of 600 mg every 12 h (1200mg/day) because of documented or suspected MDR Gram-positive bacterial infections.2 Patients with history of cardiac, pulmonary, hepatic, renal or any metabolic disorder, chronic alcoholism, mental illness and with pathological blood cell count at baseline were excluded from the study. The patient selection criteria were consecutive type based on inclusion and exclusion criteria. Sample size was calculated considering incidence of haematological toxicity of 50% and absolute error of 10 and coefficient of correlation (r) as 0.5.

After obtaining informed consent from each patient the following data were retrieved: demographics, type of infection, microbiological isolates, duration of treatment, linezolid daily dosage (1200mg/day) and its plasma exposure. In this study, the rate of reduction between the initiation and the end of treatment with linezolid was calculated for the haemoglobin value, platelet count and WBC count. From Day 1 after starting therapy with LNZ, eligible patients underwent evaluation of haematological (haemoglobin, platelets, WBCs), renal (as serum creatinine), and hepatic (as serum transaminases status, together with an assessment of drug C min values. These evaluations were repeated once a week or in concomitance with the development of an adverse event up to the end of LNZ therapy. Any relevant information on the clinical status of the patient was also recorded.

The safety outcome was assessed by episodes of anaemia (Hb%<11gm/dl), leucopenia (defined by a white blood cell count <2500cells/mm³) and/or thrombocytopenia (platelet count <1.25lac/mm³) as per world health organization (WHO) toxicity grading scale. ^{10,11}

Pharmacokinetic evaluation was done by collecting blood sample from all patients 12 h after the last drug intake (a time window of ± 5 min will be considered acceptable), immediately before

the next morning LNZ administration (trough concentrations). ¹² All samples were centrifuged at 3000×g for 5minutes and plasma was separated and stored at -20°C. Plasma LNZ concentration was determined using a validated high-performance liquid

chromatographic (HPLC) method.¹³ Patients were defined as recovered if there was no clinical, biological and/or radiological evidence of infection at the end of treatment and as cured if this status was further confirmed at follow-up. Failure was defined as any discontinuation of linezolid therapy before the end of treatment, either because of toxicity or because of persistence of infection.

Statistical analysis

The collected data on different parameters were analysed and presented in mean ±Standard Deviation (mean±SD) at different time intervals. Normality of data were performed by Kolmogorov Smirnov test, follows normal distribution. The parametric dependent 't' test was applied to see the difference among different time

intervals. The statistical significance was set at 5% level of significance. (p<0.05).

RESULTS

Total 30 patients were included in this observational study, majority were male (80%) patients. Baseline characteristics are listed in Table 1. Mean (SD) age was 50.73 years (10.63), body weight 64.33 kg (4.89) and mean (SD) total dose linezolid given was 23.24 (3.61). All the patients received 600 mg dose of linezolid every 12 hrly, through oral or intravenous route. Linezolid was mainly administered for treatment of diabetic foot infection, infected ulcer, deep seated abscess, cellulitis, gluteal abscess and paronychia. The main indication was a suspected or proven resistant gram-positive infection like MRSA, VRSA and VRE.

Table 1: Characteristics of 30 patients included in the study.

Variable	Number of patients	Percentage of sample
Male	24	80.00
Female	6	20.00
Different variables		
Variable	Mean (SD)	95%CI
Age	50.73 (10.63)	46.76
Body weight (kg)	64.33(4.89)	62.51
Linezolid total dose (gm)	23.24 (3.61)	21.89
Diagnosis wise distribution		
Diagnosis	No of sample	% of sample
Callulitie	2	
Cellulitis	2	6.67
Deep seated abscess	3	10.00
Deep seated abscess	3	10.00
Deep seated abscess Deep soft tissue infection	3 2	10.00 6.67
Deep seated abscess Deep soft tissue infection Diabetic foot infection	3 2	10.00 6.67 53.33
Deep seated abscess Deep soft tissue infection Diabetic foot infection Gluteal abscess	3 2	10.00 6.67 53.33 3.33

Table 2: Comparison of baseline, day 7, day 14 and day 21 with respect to platelet counts by dependent t test.

Time points	Mean	Std. Dv.	Mean diff.	SD diff.	% of change	Paired t	p-value
Baseline	2.45	0.48					
Day 7	2.12	0.45	0.34	0.23	13.72	7.9260	0.0001*
Baseline	2.45	0.48					
Day 14	1.90	0.53	0.55	0.33	22.42	9.0196	0.0001*
Baseline	2.55	0.51					
Day 21	2.00	0.38	0.55	0.26	21.39	9.8576	0.0001*
Day 7	2.12	0.45					
Day 14	1.90	0.53	0.21	0.19	10.08	6.3093	0.0001*
Day 7	2.25	0.45					
Day 21	2.00	0.38	0.25	0.15	11.09	7.9663	0.0001*
Day 14	2.13	0.43					
Day 21	2.00	0.38	0.13	0.09	5.97	6.3838	0.0001*

*p<0.05.

There was significant reduction in platelet count seen from baseline to 21days (p<0.001) (Table 2). Of the 30 patients 8 patients showed decrease in platelet count, 3 patients showed decrease in haemoglobin value when compared to baseline value with p <0.0001 (Table 3) and

there was 13% reduction in WBC count in all patients on day 14 when compared to baseline (p<0.001) (Table 4) indicating haematological toxicity according to WHO toxicity grading scale. ^{10,11} These episodes appeared after a median of 14days of linezolid treatment.

Table 3: Comparison of baseline, day 7, day 14 and day 21 with respect to haemoglobin (gm/dl) by dependent t test.

Time points	Mean	Std. Dv.	Mean diff.	SD diff.	% of change	Paired t	p-value
Baseline	12.30	0.85					
Day 7	11.40	0.64	0.90	0.68	7.32	7.2303	0.0001*
Baseline	12.30	0.85					
Day 14	11.20	0.80	1.10	0.94	8.97	6.4383	0.0001*
Baseline	12.18	0.88					
Day 21	23.58	31.50	-11.40	31.81	-93.54	-1.6802	0.1077
Day 7	11.40	0.64					
Day 14	11.20	0.80	0.20	0.40	1.78	2.8180	0.0086*
Day 7	11.53	0.65					
Day 21	23.58	31.50	-12.05	31.57	-104.53	-1.7903	0.0878
Day 14	11.51	0.65					
Day 21	23.58	31.50	-12.06	31.62	-104.78	-1.7895	0.0880

^{*}p<0.05.

Table 4: Comparison of baseline and 14 with respect to WBC counts baseline (×103cells/ul) by dependent t test.

Time points	Mean	Std. Dv.	Mean diff.	SD diff.	% of change	Paired t	p-value
Baseline	5.68	0.66					
Day 14	4.94	0.93	0.74	0.93	13.03	4.3591	0.0001*

^{*}p<0.05.

Table 5: Comparison of baseline, day 7, day 14 and day 21 with respect to linezolid plasma concentration by dependent t test.

Time points	Mean	Std. dv.	Mean diff.	SD diff.	% of change	Paired t	p-value
Baseline	4.56	0.26					
Day 7	5.60	1.47	-1.04	1.36	-22.88	-4.2052	0.0002*
Baseline	4.56	0.26					
Day 14	6.33	2.68	-1.77	2.57	-38.89	-3.7770	0.0007*
Baseline	4.50	0.26					
Day 21	4.76	0.30	-0.27	0.29	-5.97	-4.3603	0.0003*
Day 7	5.60	1.47					
Day 14	6.33	2.68	-0.73	1.28	-13.03	-3.1221	0.0040*
Day 7	4.76	0.30					
Day 21	4.76	0.30	0.00		0.00		
Day 14	4.76	0.30					
Day 21	4.76	0.30	0.00		0.00		

^{*}p<0.05.

Comparison of plasma concentration of linezolid (C min) at baseline, day 7 and day 14 (Table 5) also showed significant increase with p value < 0.001. Of 30 patients 8 (26.66%) patients who subsequently developed drug related haematological toxicity at the end of 14days were

found to have high plasma linezolid concentrations (C min >10 mg/L). There was also significant increase in serum creatinine value (mg/dl) from baseline to 21days (p<0.001). However, in ALT (IU/L) and AST (IU/L) no significant change was observed.

When assessing patients in terms of clinical outcome, high recovery rate was observed in 22 patients (73.3%) and discontinuation of therapy was necessary in 8 (26.66%) patients due to severe haematological toxicities. Other mild side effects like nausea (30%), diarrhoea (13.33%), dyspepsia (6.67%) and vomiting (3.33%) were also noted. All episodes were resolved after linezolid withdrawal.

DISCUSSION

Linezolid, a prototype member of the oxazolidinones, is a commonly prescribed antibiotic in hospitals because of its excellent activity against drug-resistant, gram-positive pathogens and its favourable pharmacokinetics. 1,2 Furthermore, it has been found that its oral bioavailability is approximately 100%, allowing a shift from the intravenous route to the oral route without dose adjustment. Linezolid inhibits bacterial protein synthesis by acting at an early step and a site different from that of other antimicrobial agents. It binds to the 23S fraction (P site) of the 50S ribosome and interferes with formation of the ternary N-formylmethioninet RNA (t-RNA f-Met) -70S initiation complex. Binding of linezolid distorts the t-RNA binding site overlapping both 50S and 30S ribosomal subunits and stops protein synthesis before it starts.² The most commonly reported adverse effects associated with linezolid are gastrointestinal disturbances, thrombocytopenia, and anemia. In a continuously growing number of patients, optic and/or peripheral neuropathy or lactic acidosis have been reported. Although it has been suggested that linezolid may interfere with mitochondrial protein synthesis, the underlying pathophysiological mechanism of these later adverse events has not been studied. 14

FDA-approved the drug linezolid to treat the following conditions: (1) vancomycin-resistant Enterococcus faecium infections, including cases with concurrent bacteraemia; (2) nosocomial pneumonia caused by S. aureus, including methicillin-susceptible (MSSA) and resistant strains, or Streptococcus pneumoniae (including multidrug-resistant strains); (3) complicated skin and skin-structure infections, including diabetic infections (DFIs), without concomitant osteomyelitis, caused by S. aureus (MSSA and MRSA), Streptococcus pyogenes, or Streptococcus agalactiae; (4) uncomplicated skin and skin-structure infections caused by MSSA or S. pyogenes; (5) community-acquired pneumonia caused by S. pneumoniae, including cases with concurrent bacteremia, or MRSA.15 One study reported that the incidence of linezolid associated thrombocytopenia was higher in patients with renal dysfunction than those with normal renal fuction.¹⁶ Another study showed though there is good clinical outcome but high rate of adverse reactions during linezolid therapy for serious infections and they also proposed a protocol for monitoring therapy in complex patients.¹⁷ One retrospective observational study suggested that the application of therapeutic drug monitoring might be especially worthwhile in about 42%

of cases with the intent of avoiding either the risk of dose-dependent toxicity or that of treatment failure. ¹⁸ No studies are done to compare the parameters from baseline till end of the treatment which is necessary to define and manage toxicities related to linezolid use in a critically ill and high-risk patient.

In present study, haematological effects were detected weekly monitoring of blood through Thrombocytopenia had a gradual onset occurring on 2nd week of start of linezolid treatment and was reversible after a week of its stoppage. During treatment with linezolid, it was necessary in 8 (26.6%) patients to discontinue the drug due to high incidence of haematological toxicity and normalisation of plasma concentration allowed for progressive recovery from toxicity was followed until the planned end of treatment with good clinical outcome. The comparison table from baseline to 14 days with respect to plasma concentration of drug showed significant increase with p<0.001 and the patients who developed haematological toxicity were having high plasma concentration of C min>10mg/L implying that this side effect was associated with the accumulation of drug or metabolite. There was no report of bleeding or any clinical complications with respect to thrombocytopenia. This fact suggests that linezolidinduced haematological toxicity, being dose-dependent, may be favoured by overexposure and may be prevented or even controlled by adjusting plasma concentrations.

The issue of oxazolidinone-related myelosuppression has been recently linked to a likely molecular mechanism and it has been suggested that oxazolidinones, similar to what happens with their mechanism of action against bacteria, may inhibit mitochondrial protein synthesis in bone marrow cells causing myelosuppression. 14,19 Interestingly, the mean half-maximal inhibitory concentration of linezolid against mitochondrial protein synthesis (IC50) in rat and rabbit heart and liver mitochondria was 4.31 mg/L. 20 Accordingly, it may be reasonably supposed that linezolid-induced thrombocytopenia might occur more frequently among patients who have linezolid plasma concentrations above this threshold value for the entire dosing interval. 21

Of the 30 patients 10% patients showed marked decrease in haemoglobin value when compared from baseline to subsequent weeks till 21days, these events may be drug related as the linezolid plasma concentration (Cmin) was found more in those patients too. One retrospective case control study concluded that the lower tolerability of linezolid in patients with end stage renal disease (ESRD), compared with those with non-end stage renal disease (NESRD), is evidenced by the higher rates of thrombocytopenia and anemia in the former group and we could get little evidence about the connection between renal function and linezolid pharmacokinetics as there was significant increase in serum creatinine level.²² A study showed that there was high frequency of thrombocytopenia (57.1%) in patients with acute or

chronic liver failure when treated with linezolide but present study did not report any significant change in the AST and ALT (U/L) concentration from baseline to 21days indicating less likely to encounter adverse events related to liver function.²³ With these observations we can state that though linezolid is safe and generally well tolerated in doses of 600mg twice daily it is necessary that complete blood count should be monitored weekly in patients receiving treatment with linezolid for 14dyas or more and therapy should be withdrawn if worsening of haematological toxicities are found. Other drug related adverse effects were usually transient and mild in severity. An application of TDM might be worthwhile with the intent of avoiding the risk of treatment failure or of dose-dependent toxicity. We suggest, further studies are needed before any definitive conclusion about major factors which may affect linezolid pharmacokinetics or pharmacodynamics. We are well aware of the methodological limitations of present study, the limited sample size, which is small to let us to illustrate specific conclusions.

CONCLUSION

In conclusion, present study suggests that linezolid is effective for patients with resistant gram positive bacterial infection at standard fixed 600mg/12hr dosage, however it is particularly important to conduct a monitoring of haematological parameters both at treatment initiation and during the course of treatment with linezolid. The capability to monitor plasma linezolid concentration (C min; trough value) once a week may lead to a significant improvement in clinical use of the drug both in terms of efficacy and tolerability and even decrease in development of drug resistance.

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institutional ethics committee

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