

Linezolid; why we should question the product information

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Scope of the lecture

An introduction to linezolid, an antimicrobial agent of increasing importance, a review of linezolid pharmacokinetics and toxicity and the role of therapeutic drug monitoring

Learning objectives

1. To understand the clinical role of linezolid
2. To gain knowledge of the dosing regimen, pharmacokinetic parameters and toxicity of linezolid
3. To understand the role of linezolid therapeutic drug monitoring in optimising efficacy and reducing toxicity in a variety of patient groups

Extended abstract

Background

Linezolid is the first oxazolidinone antibiotic licensed for clinical use. It exhibits *in vivo* and *in vitro* activity against resistant gram positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE). In addition linezolid is playing an increasingly important role in the management of multidrug resistant tuberculosis (MDR TB), extensively drug resistant TB (XDR TB) and unusual infections such as nocardiosis which are diagnosed with increased frequency, in particular in immunocompromised patients. At our institution, a tertiary university hospital with a complex patient mix, prescription of linezolid and expenditure on this agent increased from \$99,266.33 in 2013 (511 tablets, 209 i-v infusions) to \$242,069 in 2016 (994 tablets, 776 i-v infusion bags) despite a price reduction mid 2016 when generic alternatives became available.

Linezolid is metabolised by oxidation of the morpholine ring. *In vitro* studies are contradictory but some suggest cytochrome P450 may play a role in metabolism. However the metabolic pathways are not

fully understood. Non-renal clearance accounts for 65% of total linezolid clearance with approximately 30% of the dose detected in the urine. The mean renal clearance of linezolid is 40mL/min suggesting tubular reabsorption. The Product Information for linezolid (Xyvox, Pfizer) states that a 'one size fits all' convenient dosing regimen of 600mg twice daily is appropriate for all adult patients regardless of weight, body mass index, age, presence of sepsis and renal or hepatic function. However the uncertainty around the metabolic pathways and variable renal clearance and tubular reabsorption would suggest that the fixed dosing regimen may not be appropriate for all patients. The Product Information also states that total treatment duration should not exceed 28 days because of the increased risk of toxicity, in particular myelosuppression and neurotoxicity. In clinical practice however patients with deep-seated infection such as osteomyelitis or endocarditis, and patients with MDRTB, XDRTB or nocardia infection often require prolonged treatment courses far exceeding the recommended 28 day maximum.

PK/PD parameters

Linezolid exhibits time-dependent activity whereby the time during which the plasma concentration exceeds the minimal inhibitory concentration (MIC) of the pathogen and the AUC_{0-24}/MIC ratio are important PK/PD parameters. $T > MIC$ of 85% and $AUC_{0-24}/MIC > 100$ are suggested for maximum antibacterial efficacy (1). It is now generally accepted that the risk of haematological toxicity, in particular thrombocytopenia, is elevated when the linezolid C_{min} is $>9\text{mg/L}$ and the AUC_{0-24} is $>400\text{mg/L}$ (2, 3). Evidence concerning the concentrations required for efficacy is less conclusive. Dong *et al* (4) reported that target attainment in critically ill patients was virtually 100% when the MIC was $\leq 1\text{mg/L}$ falling to 0% for $MIC \geq 2\text{mg/L}$ at standard dosing. The inter-patient variability of linezolid is highlighted in Figure 1, reproduced with permission from Cattaneo *et al* (5) which clearly demonstrates the wide range of serum concentrations at first TDM measurement in 150 patients receiving linezolid at a standard dose of 600 mg twice daily.

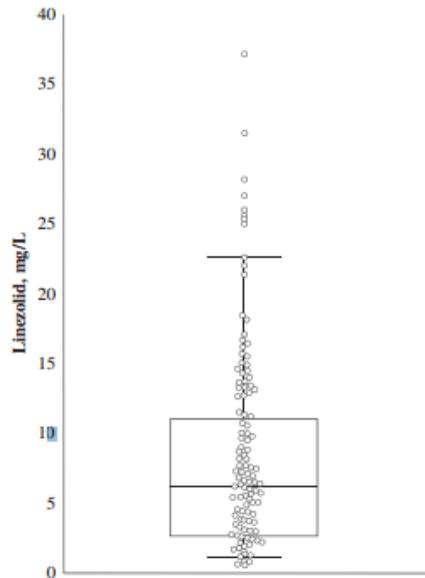


Figure 1. Distribution of linezolid (LZD) plasma trough concentrations measured at the first TDM assessment in 150 patients given the drug at 600 mg bid [15,16].

The significant inter-individual variability in linezolid pharmacokinetics and relatively narrow therapeutic index suggest a need for linezolid therapeutic drug monitoring (TDM). There have been a number of publications which have indicated TDM of linezolid may be useful to optimize efficacy and minimize toxicity in a variety of clinical settings. Representative articles include:-

1 Altered renal function

- Matsumoto *et al* (6) – higher rates of haematological toxicity in patients with renal impairment.
- Nukui *et al*), (7), Tsuji *et al* (8) – high plasma linezolid concentrations and impaired renal function associated with thrombocytopenia.
- Villa *et al* (9) – a review of the impact of continuous renal replacement therapy on linezolid pharmacokinetics. Extracorporeal clearance varied according to the filtration modality with suboptimal AUC/MIC ratio in 8/9 studies for a pathogen with an MIC of 4mg/L.

2 Critically ill patients

- Dong *et al* (4) – a study of 27 critically ill patients receiving linezolid. Monte Carlo simulation indicated target attainment was unlikely in this patient group if the MIC were >1mg/L

- Topper *et al* (10) – highly variable linezolid exposure in 20 critically ill patients with PK drug interactions contributing to variability; proton pump inhibitors correlated with increased exposure and levothyroxine associated with very low exposure.
- Taubert *et al* (11) – the presence of Acute Respiratory Distress Syndrome newly identified as a strong predictor of inadequate linezolid concentrations.

3 Body weight

- Abe *et al* (12) – large population PK study. Body weight significantly influenced clearance and volume of distribution.
- Bhaloodi *et al* (13) – standard doses for patients weighing up to 150kg should be adequate
- Corcione *et al* (14) – two morbidly obese patients who failed to achieve adequate PK parameters despite increasing the dose to 600mg three times a day.

4 Age

- Cattaneo *et al* (15) – elderly patients had linezolid concentrations 3 times higher than those <40 years
- Tinelli *et al* (16) – dose reduction of linezolid reduced toxicity in patients >70 years while maintaining trough concentration within the therapeutic range

Studies correlating linezolid concentration with toxicity and outcome are summarised in the table below, reproduced with permission from Cattaneo *et al* (5).

Table 3. Summary of studies dealing with the potential associations between TDM of LZD and clinical outcome.

Reference	Study design	Patients	Role of TDM
Matsumoto et al. [19]	Retrospective	11 patients given LZD for any reason	Patients with thrombocytopenia had LZD $C_{min} > 14.4$ mg/L and $AUC_{0-24} > 513$ mg · h/L
Hiraki et al. [48]	Retrospective	8 patients with pneumonia	Patients with thrombocytopenia had LZD $C_{min} > 22.1$ mg/L
Peat et al. [41]	Retrospective	45 patients given LZD for any reason	Patients who had with had LZD $C_{min} > 6.5$ mg/L or $AUC_{0-24} > 280$ mg · h/L had >50% probability to experience thrombocytopenia
Cattaneo et al. [15]	Prospective, observational	50 patients given LZD for any reason	Patients with thrombocytopenia had LZD $C_{min} > 9.0$ mg/L
Nukui et al. [22]	Prospective, observational	30 patients given LZD for any reason	LZD $C_{min} > 7.5$ was associated with an odds ratio of 90 ($P < 0.0001$) to experience thrombocytopenia
Matsumoto et al. [23]	Retrospective	44 patients given LZD for any reason	The threshold for LZD C_{min} to minimize drug-induced thrombocytopenia was 8.2 mg/L
Dongh et al. [52]	Retrospective	70 critically ill patients	LZD $C_{min} > 2$ mg/L was associated with >80% bacterial eradication; LZD $C_{min} > 6.3$ mg/mL was associated with >50% thrombocytopenia.

Linezolid TDM at St. Vincents Hospital, Sydney

St. Vincent's Hospital, Sydney is the state referral centre for heart, lung and bone marrow transplantation and also performs renal transplantation. In addition the hospital houses one of Australia's leading and largest HIV medicine units and cares for a growing population of marginalised patients including intra-venous drug users and the homeless. With the complex patient mix treatment courses of linezolid at our institution frequently exceed the 28 days maximum recommended duration. We recently analysed the results of linezolid TDM for all patients receiving oral linezolid from January-December 2016 to ascertain the impact of TDM on treatment dose and toxicity and to determine cost savings attributable to TDM. Twenty seven patients received 32 courses of linezolid, with 26 courses undergoing linezolid TDM. Based on the results 11/26 (42%) underwent a dose reduction with a total theoretical reduction in expenditure of \$103,169 based on an overall 40% decrease from the standard recommended dose of 600 mg twice daily. One patient (a lung transplant recipient with disseminated nocardia infection) received 9 months of therapy. At a dose guided by TDM of 150mg twice daily, this patient experienced no haematological or other toxicity over the 9 month period and the reduced dose resulted in savings of \$61,245 when compared with standard dosing. Overall, 9 patients received ≥ 28 days therapy (range 31-252, mean 79). Of the 7 evaluable patients only one patient (concurrently receiving chemotherapy for a haematological malignancy) had a platelet count $< 100 \times 10^9/L$ at the end of therapy. In our patient group, TDM is a highly cost-effective intervention to both reduce drug costs and minimize patient toxicity. We were able to reduce the standard dose of linezolid by 50-75% whilst

maintaining adequate trough concentrations, resulting in significant savings to the healthcare system and reducing treatment-limiting toxicity.

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