Therapeutic Drug Management of Linezolid for Optimizing Efficacy and Minimizing Toxicity

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Scope of the lecture:
This lecture is focused on the therapeutic drug management (TDM) of linezolid to optimize efficacy while minimizing the toxicity.

Learning objectives:
1. Wide inter individual variability seen with the traditional linezolid dosing regimen
2. Clinical covariates explain only a part of this variability
3. Clinical relevance of linezolid TDM

Extended abstract:
Linezolid is an oxazolidione with strong activity against multi-drug resistant Gram-positive cocci, methicillin-resistant *Staphylococcus aureus* (MRSA) and *vancomycin-resistant enterococcus* (VRE). Linezolid plasma exposure following the administration of the traditional dose of 600 mg every 12 h may result in large inter individual variability. Some clinical covariates such as body weight, age, renal function and co-medications can explain part of this variability.

Linezolid demonstrates time dependent antimicrobial activity; optimal antimicrobial effect is achieved when the linezolid concentration is above the minimum inhibitory concentration (T>MIC) of the infecting pathogen for 85% of the dosing interval. Hence, linezolid efficacy is related to therapeutic target of AUC (area under the concentration-time curve over 24 h) divided by the MIC and AUC/MIC >120 $mg \cdot L^{-1} \cdot h^{-1}$ is needed to treat most sites of infection. For MICs ≥2 mg/L, with the traditional dosage regimen probability of target attainment is poor and the suboptimal exposure may result in aggravation of infection, emergence of resistance, and increased mortality. Patients requiring higher doses and prolonged treatment are at higher risk of over-exposure to linezolid. Linezolid toxicity (thrombocytopenia and anemia) is related to AUC and duration of linezolid treatment. Hence, given the wide variability in linezolid exposure and difficulty of managing the treatment of critically-ill patients, therapeutic drug management (TDM) of linezolid may be helpful in optimizing the exposure for maximizing effectiveness while minimizing toxicity.

Numerous studies have found good linear relationship between linezolid trough concentration (Cmin) and the estimated AUC24. Hence, several studies have proposed Cmin as a useful predictor of linezolid exposure. However, Cmin values for useful for linezolid efficacy have to take the MIC into consideration. The AUC24 can be estimated on measured Cmin and Cmax values using a Bayesian estimator (e.g. BestDose, ADAPT) that is able to handle the dose related non-linearity see with linezolid. Sampling should be performed just before the

dose (Cmin) and sample taken 30 minutes following 1 hour infusion for intravenous dose or 2 hours following oral dose (Cmax) of linezolid.

AUC24/MIC is a better target as this takes the MIC of infecting pathogen into consideration providing the clinician the flexibility to aim at higher exposure rates initially to improve treatment efficacy. While TDM will help lower the risk of exposure dependent linezolid toxicity.

References