Oxazolidinones: In vivo Efficacy Determinants & Interaction with Cyanobacterial Extracts

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AIMS & OBJECTIVES

1. To set up models of infection in mice with MRSA, VRE and *S.pneumoniae*.
2. To investigate ED_{50} of Linezolid and Cyanobacterial extracts in these models and compare it with Vancomycin and Synercid.

3. To determine the most suitable route of administration of these drugs.
4. To establish the PK/PD parameters predicting *in vivo* efficacy.

Summary & Conclusions

1. Treatment of Gram-positive bacteria constitutes the unmet medical needs of clinicians. There has been a lacuna in the availability of newer antimicrobial treatment options because most of the bacteria are acquiring resistance to the available treatment options. Oxazolidinones constitute a new class of antimicrobial agents, which have been made available in the clinic after a gap of 35 years. The understanding generated with this class of antimicrobial is very limited. Linezolid is the first Oxazolidinone that has been marketed by Pharmacia (now merged with Pfizer) in the year 2000. Though a wealth of data has been generated by the parent company on the activity potential of this compound but it is limited only to the isolates from western countries.

2. The research work presented in this thesis concerned the exploration of antibacterial potential of oxazolidinones in animal models of infection. We decided to explore the antibacterial potential of this antibacterial class against gram-positive clinical isolates of Indian origin on one hand and part of this work also constituted investigation of cyanobacterial extracts as potential source of antibacterial compounds.

3. In support of the first objective animal models of infection were established with clinical isolates of MRSA, CoNS, VRE and *S.pneumoniae* in Swiss Albino mice. Besides systemic infection models, target organ specific models were established with the indicator pathogens to mimic clinical course of infection. For example, to mimic skin & soft tissue infection murine air pouch infection with *S.aureus*, to mimic catheter infection, catheter infection model with *S.epidermidis* and to

mimic respiratory infection pulmonary infection model with *S.pneumoniae*.

4. For fulfillment of second and third objective, in vivo antibacterial activity of linezolid was established in animal models by oral and parenteral route in comparison with suitable standard drugs. Vancomycin is the drug of choice in clinic for Gram-positive bacteria and synercid is a new streptogramin that has been in clinical use since 1997. Linezolid was observed to be the best antibacterial agent showing efficacy at very low doses for the treatment of murine staphylococcal infections, while vancomycin exhibited better activity against Enterococcal infections. However, vancomycin could not cure infection caused by Vancomycin-resistant enterococci, while linezolid was effective against these pathogens.

5. While investigating the antibacterial potential of cyanobacterial extracts from a limited number of cyanobacterial isolates, lipophilic extracts were shown to exhibit antibacterial activity, however, this activity was not quantifiable with the methodology available in our laboratory. Therefore, the conclusion was that this activity needs to be optimized in a separate study wherein; natural product chemistry expertise is required. This expertise was beyond the scope of the present study.

6. To determine the optimal route of administration of oxazolidinones, oral and parenteral route of treatment was used for many of the experiments. The conclusion drawn was that linezolid exhibits similar activity by both the routes. This finding was in concordance with the published data for linezolid. This drug therefore, would qualify for oral- to- IV switch therapy and patients hospitalized with serious gram-positive bacterial infection can be discharged earlier.

7. To decipher the PK/PD correlates of efficacy, linezolid and Ranbezolid were used as test drugs. The pharmacodynamic relationship between linezolid treatment and outcome as assessed by ED_{50} in systemic infection caused by *S.pneumoniae* and vancomycin-sensitive & resistant *E.faecalis* led to the conclusion that linezolid would be more effective if administered more frequently. Effect of dosing frequency was also observed in thigh infection caused with MRSA and *S.pneumoniae*. Bacterial load in animals treated with single dose of linezolid matched with those of untreated controls at the end of 12-24 hours post infection, whereas, bacterial growth remained static in animals that were given an additional dose at 4 hour post infection. These experiments suggested that the drug should be in circulation for a long period to show better efficacy. This finding was in concordance with the single published report that t>MIC could be the predictor of efficacy for linezolid. When Ranbezolid was used as a test drug for PK/PD determination for MRSA infections, both t>MIC and AUC/MIC ratio were found to correlate with decrease in bacterial load suggesting that both the parameters could be the predictors of efficacy.